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CONTENTS

	PAGE
On the Prognosis of Cretinism. DAVID LAWSON	75
The Absorption of Short-chain Fats by Premature Infants. SELMA E. SNYDERMAN, SOLEDAD MORALES and L. EMMETT HOLT, JR.	83
A Study of Cerebral Palsy in the Childhood Population of Edinburgh. T. T. S. INGRAM ..	85
Congenital Pneumonia and Pneumonia in the Neonatal Period. KR. HARNAES and K. H. TORP ..	99
Haemoglobin and Red Cells in the Human Foetus: II. The Red Cells. ELIZABETH P. N. TURNBULL and JAMES WALKER	102
Haemoglobin and Red Cells in the Human Foetus: III. Foetal and Adult Haemoglobin. JAMES WALKER and ELIZABETH P. N. TURNBULL	111
Blood Formation in Infancy: Part III. Cord Blood. JOHN MARKS, DOUGLAS [illegible] and JANET D. ROSCOE	117
The Use of Cobalt in Some Common Anaemias of Childhood. B. L. COLES	121
The Determination of Blood Pressure in Infants by the Flush Method. JOHN RAINSFORD and MICHAEL PYM	127
Circulating Basophilic Leucocyte Counts in the Newborn. ROSS G. MITCHELL	130
The Evaluation of the Eosinopenic Response to Corticotrophin and Cortisone in the Newborn Infant. JAMES W. FARQUHAR	133
The Effect of Disease and Injury on the Adrenal Cortex of Stillborn and Newborn Infants. F. A. LANGLEY and J. C. BURKE	141
A Case of Galactosaemia with Special Reference to Mental Development. P. [illegible] GRAY and C. T. POTTER	147
The Amino-aciduria in Galactosaemia. D. E. CUSWORTH, C. E. DENT and F. W. [illegible] ..	150
A Study of the Genetics of Galactosaemia. A. HOLZEL and G. M. KOURIES	155
A Familial Tubular Absorption Defect of Glucose and Amino-acids. JOSEPH [illegible] and WILFRID SHELDON	160
A Case of Hypothyroidism with Pseparucaleinosis. JEAN M. NAYLOR	165
Metastatic Tuberculous Abscesses. F. J. W. MILLER and MAUREEN CARRIGAN	169
Bile Peritonitis in Infancy. PAMELA A. DAVIS and A. ELLIOT-SMITH	174
Superficial Gangrene of the Skin in Chickenpox. R. S. ILLINGWORTH and [illegible] ZACHARY ..	177
Subacute and Chronic Intussusception in Infants and Children. DUNCAN MACKENZIE and THOMAS MOORE	180
Gangrene of the Extremities in Two African Infants. LORNA G. MACDONALD	184
A Case of Fibroma of the Left Ventricle in a Child of 4 Years. URSULA JAMES and MARGARET H. STANFIELD	187
Family Periodic Paralysis in a Mentally Defective Boy. THOMAS A. COUPER	193
Pellagra in an English Child. G. W. HICKEY	195
Paediatric Societies in the British Isles	197
Book Reviews	198

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ON THE PROGNOSIS OF CRETINISM

BY

DAVID LAWSON

From The Hospital for Sick Children, Great Ormond Street, London

(RECEIVED FOR PUBLICATION SEPTEMBER 15, 1954)

History of the Recognition of Sporadic Cretinism

Endemic cretinism, and its association with endemic goitre, or 'bronchocoele', have been known for many centuries, but sporadic cretinism occurring in non-endemic areas was first clearly described as a separate entity by Fagge in 1871.

Absence of the thyroid gland was first observed by Curling (1850) at necropsies upon two typical cretins. He commented that the association of the features of cretinism both with enlargement of the gland, as in endemic cretinism, and with its total absence, as in these two cases, could hardly be a coincidence. Fagge (1871) in his original description of sporadic cretinism carried this line of argument further in putting forward the speculative but correct hypothesis that the hypertrophy in endemic cretinism represented an unsuccessful attempt to 'protect against the more severe defects of the endemic influence': if this attempt were unsuccessful the end-results might be the same as those of a congenital defect. One of Fagge's four cases had been normal until an attack of measles at the age of 8, after which signs of hypothyroidism developed. This observation led him to predict the symptomatology which might result were the disease to supervene in adult life. Three years later his predictions were fulfilled in Gull's (1874) description of the first two cases of what was later called 'myxoedema', in a paper entitled 'On a Cretinoid State Supervening in Adult Life in Women'. In 1878 Ord described a necropsy on such a case, in which fibrotic changes were present in the thyroid gland. He thought that the intercellular substance deposited in the subcutaneous tissues was a mucin, and that its accumulation was due to the failure of the thyroid gland to perform its postulated normal function of excreting mucin. He suggested the term 'myxoedema'. This name has clung, although both the suppositions on which it was based—on the nature of the intercellular material and on the function of the thyroid—were very soon proved false.

Kocher (1883) reviewed a series of 101 thyroidectomies with an operative mortality of just over 10%, and good short-term results in the other 90%. While carrying out these operations he had concurred in the common view that the thyroid gland was functionless in man. When the subsequent development of a cretinoid state in one of his patients was brought to his notice he followed up the 24 of his patients in whom thyroidectomy was thought to have been complete. Six were well, two could not be traced. The other 16 cases had followed a common path. The symptoms, developing four to five months post-operatively, were those now recognized as characteristic of myxoedema. In particular he noted that children so affected were miserable when, after operation, they lost their places in school life and were overtaken in mental development by their younger siblings. The similarity to cretinism was recognized, but identity was not claimed and the term 'cachexia strumipriva' was coined. In the same year Reverdin and Reverdin (1883) described similar results in a series of 20 cases, but remarked that the disorder simulated that described by Gull and by Ord (myxoedema) even more closely than cretinism.

Considerable interest was stimulated by these findings, and by Schiff's (1884) report on the effects of thyroidectomy in animals, and a committee of the Clinical Society of London was appointed to investigate the relationships of sporadic cretinism, myxoedema and cachexia strumipriva. This committee (1888) reported that the last two were identical and that cretinism was myxoedema occurring in childhood. Victor Horsley (1892) reviewed an experimental programme which he had carried out on behalf of this committee. The clinical picture of the experimental disease was still confused by incidental parathyroid removal, but as a result of his studies Horsley put forward the following view of the function of the thyroid gland.

A colloid was secreted by the thyroid gland into its vesicles, and was discharged into the blood stream via the lymphatics. This secretion was essentially connected with the metabolism of blood and tissues, but not specifically with that of the brain.

The gland was functionally active before birth. In the study of the comparative pathology of thyroidectomy in various species, Horsley found that it had no effect on birds or rodents; in ruminants the syndrome was slow to develop. In man and monkeys the disease was of moderate severity; it was most severe of all in carnivora. The symptoms of the experimental disease, which often took weeks or months to develop, could be precipitated by exposure to cold or by the giving of meat extracts.

The clear association of these symptoms with absence or non-functioning of the thyroid gland cleared the way for attempts at replacement therapy.

Schiff (1884) had shown that in animals the subcutaneous implantation of thyroid tissue could temporarily protect against the effects of thyroidectomy, and Horsley (1890) suggested the application of this method to the treatment of myxoedema in man. This advice was followed by Bettencourt and Serrano (1890) who implanted part of a thyroid gland subcutaneously in a woman of 36 suffering from myxoedema. Improvement started within 24 hours and thereafter she quickly lost all symptoms of the disease; it was properly concluded, from the rapidity of cure, that the effects must have been due to the absorption from the implanted gland of pre-formed secretion, as there had not been time for the graft to vascularize. Murray (1891 and 1892) then tried the subcutaneous injection of a glycerine extract of sheep's thyroid. 'As the secretion normally passed into the blood mixed with the lymph I decided, in testing the efficiency of the extract, to inject it beneath the skin so that it might be absorbed by the lymphatics and so enter the blood as nearly as possible under normal conditions' (Murray, 1900). This remedy was effective, but it was soon shown simultaneously by Mackenzie (1892), and by Fox (1892), that the extract could be given orally with equally good effect. There is an interesting phylogenetic explanation of the efficacy of thyroid by mouth, in that in more primitive species the thyroid gland discharges its secretion directly into the gastrointestinal tract via the thyroglossal duct.

The first recorded case of the use of thyroid gland in the treatment of cretinism is probably that of Byron Bramwell (1894).

In 1896, when substitution therapy in hypothyroidism had been in use for five years, cretinism was discussed at the annual meeting of the British Medical Association (*Brit. med. J.*, **1**, 661, 1896). Some of the problems surrounding the management of cretinism had already begun to emerge. The efficacy of substitution therapy was agreed, but perhaps because the first group of cases were long-standing defectives, little reference was made to the mental prognosis, although it is probably from this time that it came to be assumed that if only the case could be diagnosed early enough the mental prognosis would be as good as the physical. At this meeting Rushton Parker noted that there was often no improvement in the legs, due to the 'softening of bones produced by thyroid extract', and Telford Smith observed that the growth of bone was so rapid that softening took place. It was left to John Thomson at the same meeting to identify this complication as the unmasking of latent rickets by rapid bone growth. His comments are worth quoting in full:

> 'When one sees the bent limbs, the changed epiphyses and sometimes a sort of rickety rosary on the chest wall, along with profuse sweating, nocturnal listlessness, and muscular debility one naturally asks oneself whether, in restoring to these adolescents the growing capacities of babyhood, we have not also given them back the liability to rickets which they had left far behind them. It seems quite probable that this may be so.'

During the last 20 years of the nineteenth century, therefore, the technique of substitution therapy in hypothyroidism became established. During the same period, work in the physiological field established the thyroid gland's requirement of, and affinity for, iodine, and showed that the active secretion of the gland was an iodine-containing globulin (Harington, 1933).

The Effects of Treatment with Special Reference to Mental Development

An excellent account of myxoedema and cretinism was given by Murray (1900), and it is here, in the final paragraph of his book, that the first authoritative reference is made to the mental prognosis in treated cretins:

> 'The intellectual development is always much slower than the bodily growth and general improvement in all other respects. The shorter the duration of the symptoms has been at the commencement of the treatment the more rapid the improvement in the mental condition, and I think it is only in cases in which the treatment is started early that we can expect normal intellectual development to take place.'

The exact phrasing used by this careful observer and writer should be noted. 'The shorter the duration of symptoms' is not exactly synonymous, as many have since assumed it to be, with 'the earlier in life', for, quite apart from the physical symptoms, a marked mental retardation, present from birth, may of itself bring the child to a physician for diagnosis before the physical signs of disease have become obvious.

Since the publication of Murray's monograph sporadic cretinism has been generally recognized in this country and thyroid extract by mouth has been the standard treatment. Nearly all writers on the subject have given a good physical and a guarded mental prognosis. There has, however, been a general tendency to make two assumptions, the validity of both of which has been questioned in recent years. The first is that mental development would be normal if the diagnosis were made and treatment instituted as early as possible in every case; and the second, that thyroid dosage should be as high as possible if the best mental development is to be achieved. Aldrich (1936) in particular advised pushing thyroid to the limits of tolerance and was critical of the generally pessimistic attitude to mental prognosis. Tredgold (1929), however, thought that there were probably two types, one in which mental retardation was due to hypothyroidism, and another in which there was 'primary amentia with superadded hypothyroidism'; and Gamper (1928) noted 'a torpor which is myxoedematous and a defect, not accessible to thyroid therapy, which is attributable to arrest of cerebral development and changes in cerebral structure'.

Thomson (1925), from a study of 21 personal cases followed for some years, anticipated in some respects the more fully documented findings of Lewis, Samuel and Galloway (1937a and b) in his description of the personality of the treated cretin: 'As he grows older . . . he develops a curious air of apathy . . . and abnormal deliberation. He knows the few things he does wish to do, and quietly insists on doing them, though he is long about it' . . . 'He takes in a great deal more of what is going on than we give him credit for' . . . 'His eyes have a steady, patient look, very different from the shifting vacant expression seen in most imbeciles.' Thomson noted that in a considerable proportion of cases the child remained an imbecile, and that under these circumstances the power of speech was almost or quite in abeyance.

In the past 20 years several papers have been published reviewing the prognosis for treated cretins. • This circumstantial testimony all leads one to believe that the basic intelligence, and perhaps certain personality defects, are fixed by the time of birth, and that all that thyroid replacement can do is to relieve the physical symptoms, and, drawing aside like a veil the 'myxoedematous torpor', reveal the individual behind, who may be normal, but who in the great majority of cases will show defects both of intelligence and of personality. • But there is as yet no study of a large series of cretins diagnosed and adequately treated from the age of 3 months, which alone can authoritatively settle the question of the effect of early treatment on mental prognosis.

Lewis *et al.* (1937a and b) made a retrospective survey of 79 cases collected from a variety of institutions and hospitals in London, all of which had been under treatment for some years. An attempt was made to assess the value of substitution therapy in the treatment of the mental retardation. The previously reported observation that slowness of the mental process was the distinguishing characteristic of the treated cretin was confirmed; it was added that these children were placid in a congenial environment but pig-headed, bad-tempered, and obstinate if crossed. Only four out of 79 were markedly depressive. A feature recorded here as a new observation, but foreshadowed in Thomson's description in 1925, is that of obsessional behaviour; many of the individuals were tidy, clean, and repetitive to an abnormal degree, and painstakingly thorough in anything they undertook. Only one in five had an I.Q. over 80, but it should be noted that this was a retrospective study and that the sources of many of the cases were mental institutions. There was no excessive scatter in the behaviour in different fields of activity, although consistently lower scores were obtained in tests in which speed was taken into account. Data on the early histories were inadequate, but it was concluded that in general the earlier the clinical onset of symptoms the worse the mental prognosis. No strict relationships could be found between the final intellectual level and either the age at which treatment had been started on the one hand or the probable adequacy with which it had been maintained on the other. Two of the more striking exceptions to these generally assumed relationships are quoted: one, a child who, following treatment from the age of 4 months, achieved a final I.Q. of 34 only, and another who was not treated until the age of 11, but whose final I.Q. was 101.

Kerley (1940) reported two cases which appeared to uphold the optimistic views of Aldrich (1936). Both were typical cretins who, following treatment from the age of 7 months and 10 weeks respectively, with thyroid grains 3 daily, were 'honours students' at the ages of 9 and 16 years. The author knew of six others who had been treated since infancy and who at ages between 16 and 40 years had 'normal mental endowment'. Without knowing the size of the series of cases from which these examples are drawn, however, no deduction as to the frequency of such happy results can be made.

McDonald, Brown and Bronstein (1940) described the background and social adjustment of 27 children who had been under treatment for seven years.

A wide range of intelligence was found, from defective to average, the majority being high-grade defectives. Most had been able to establish habits in accordance with those of normal children of the same mental age. The authors concluded that glandular therapy did not overcome low intelligence or unwholesome parental attitudes.

Goodkind and Higgins (1941) studied 23 children who had been under sustained treatment for from five and a half to 24 years. All except one of the cases had shown evidence of the disease in the first year of life and were therefore presumably congenital cretins. In all cases the diagnosis was confirmed by interruption of treatment. Six had I.Q.s of 90 to 112, six of 70 to 89, and 10 of below 70 (one of 20, one of 15). The ages at diagnosis and beginning of treatment were usually much earlier in the ultimately mentally retarded cases than in those of normal intelligence. Evidence is given that thyroid grains $1\frac{1}{2}$ daily will raise to normal the basal metabolism of the athyreotic patient over the age of 6 years. The degree of thyroid deficiency, as measured by the amount of thyroid necessary to maintain normal metabolism, was not proportional to the degree of mental retardation. It was concluded that the cerebral deficiency could probably be regarded as congenital and from the same cause as the thyroid damage. The value of serum cholesterol estimations was studied and it was found that the cholesterol level correlated closely with the B.M.R. When treatment was interrupted to confirm the diagnosis the serum cholesterol level rose significantly within one month in 75% of cases, and within two months in all.

Bruch and McCune (1944) made a psychiatric study of 23 cases selected for adequacy of records, and of physical response to treatment. The diagnosis was confirmed in each case by interruption of treatment. Intellectual development is described as proceeding under treatment without increase in I.Q. in all cases but one. The importance of this observation is, however, diminished, as the authors concede, by the fact that the first psychometric examination was carried out many months, and sometimes years, after treatment had started. Neither the age at the beginning of treatment nor the regularity thereof are considered to correlate with mental prognosis, but it is noted that if treatment is delayed beyond the age of 3 years full stature may not be achieved. Valuable comments are made upon three individual cases. The best child, who achieved a final I.Q. of 112, had been treated from the age of 5 months, but had been noted to be 'bright' before treatment, although of typically cretinoid appearance. The story of a second case suggests strongly that over-dosage with thyroid, apart from failing to improve the intelligence, may lead to neurotic disturbances and thus interfere with the best use of limited mental equipment. A third child was observed to perform skilled acts better with no thyroid at all than on a previously excessive dose. It was concluded that mental development showed considerable independence of treatment, and that functional development before treatment began was the best index of capacity for future progress: that the optimal dosage of thyroid must be found by experiment in each case, bearing in mind that thyroid in excess of the requirements for physical response has a 'disrupting influence on the personality and on integration'; and that by the time of birth the 'potentiality for mental development has become independent of the activity of the thyroid gland'.

Radwin, Michelson, Berman and Kramer (1949) made a similarly careful clinical and psychometric study of 12 adequately proved cases, which had been observed for from 13 to 23 years, usually since infancy, and who were currently aged 13-26 years. An average dose of 2 to 3 grains a day had been given throughout the period. Seven cases had I.Q.s of 82 to 103, two of 77. These nine cases had all made satisfactory social adjustments and were useful members of society. The I.Q.s of the other three were 42, 57, and 67 respectively. Physical development had been normal in all cases. Although most of the rise in I.Q. occurred in the first three years, significant rises were observed after this period had elapsed in two-thirds of the cases. Behaviour characteristics are described which are mildly abnormal and which are present irrespective of the level of intelligence. The speech is hesitant and slurring, movements and gait are slow; some are euphoric and emotionally labile. They are better at manual than at intellectual work. 'Their mannerisms, attitudes and emotional characteristics were not those of fully normal adolescents or adults.'

Cretinism at The Hospital for Sick Children, Great Ormond Street, 1917-1938

An attempt was recently made to follow up a series of cretins treated at The Hospital for Sick Children between 1917 and 1938. No out-patient records are available for this period, during which only 36 cases were admitted. Seven of these children died while in hospital. Of the other 29, only five could be traced. One of these had died shortly after discharge. The other four were re-examined in 1953. Although this material is quite inadequate for the study of the series as a

whole, it so happens that these four cases illustrate well some of the vagaries of the disease.

Case Reports

Case 1. I.G., a girl (No. 219102), first walked at the age of 2 years and 3 months and had just begun to talk at the age of 3 when it first occurred to her mother that she was 'backward'. The diagnosis was made, and treatment was started at the age of 4 when she had whooping cough. Treatment changed her whole appearance and behaviour for the better; she learned to talk properly in a few months, and gained six inches in height in the first year. She was admitted to Dr. Poynton's ward in 1924 at the age of 9 years and 3 months (weight 41 lb., height 40½ in.). There was no evidence of cretinism at this time. She was later looked after by Dr. Tredgold at University College Hospital, who increased the thyroid to 8 grains a day but had to reduce it again as the pulse rate went too high. She was educated at a special school and was always backward.

She had always lived with her mother, who attended with her in 1953, and who said that she was normally behaved at home, but could take no responsibility and needed 'constant probing'. Her vocabulary, conversational responses, and appearance were normal. Menstruation had begun at the age of 15 and had always been normal and regular. The epiphyses were normally fused. Her I.Q. is 96.

In this case there is good evidence that treatment with thyroid has been adequate. Her formal intelligence is within the normal range, and her social inadequacy must be attributed to a defect of personality rather than of intelligence.

Case 2. C.M., a girl (No. 219105), was brought to hospital by her mother on account of failure to sit up; she was diagnosed by Dr. Cockayne at the age of 1 year and 1 month and treatment was started. It was apparently not adequately maintained, for on admission to Dr. Poynton's ward in 1927 with pyrexia of unknown origin at the age of 2¾ years, she was stunted and fat, the skin was dry, the anterior fontanelle was open and only four teeth had erupted.

She attended with her mother in 1953. She had not begun to talk until the age of 3½ years. She can neither read nor write, but plays the piano excellently by ear. She is helpful about the house but would not be capable of independent life. She is very methodical, never leaves anything out of place, and is meticulous about her personal appearance. Menstruation began at the normal time and has always been regular. The epiphyses have fused normally. Her I.Q. is 39.

This child, who is severely defective, shows well the obsessional behaviour described by Lewis,[4] and also illustrates the dissociability of intelligence and musical ability.

Case 3. A.S., a boy (No. 211916), was always backward. He sat up at 4 years and began to walk stiffly at the age of 5 years. He was treated intermittently from the age of 6 years, but when admitted to Dr. Paterson's ward in 1935 at the age of 10 was a 'typical cretin'. Treatment with thyroid was started then and has been continuous since.

He attended with his parents in 1953. Although showing no cretinoid features, he is obviously defective. He understands the spoken word but is totally dumb. He has a fairly well developed sign language. His hands, but not his arms, are in continuous repetitive movement, and he wears an anxious expression. There is a mild spastic quadriplegia.

He is markedly obsessional. He takes his clothes off tidily, folding them up neatly one by one and will wander round the house picking up little bits of thread and paper and putting them into a wastepaper basket. The epiphyses are normally fused. His I.Q. is 25.

This boy, the most defective of the four, shows the most marked obsessional behaviour and 'the power of speech', as Thomson (1925) noted in some of his cases, 'is in abeyance'.

Case 4. I.D., a boy (No. 219114), was noticed to be backward at the age of 6 months and was treated intermittently with thyroid until the age of 3 or 4, since when treatment has been continuous and adequate. He was admitted to Dr. Thursfield's ward in 1935 at the age of 1½ years when he had a typically cretinoid appearance, and ossification was delayed: he lost weight rapidly on treatment with thyroid; for most of the third year of life he was in hospital with 'tuberculosis of the spine', and wedging of the second lumbar vertebra was radiologically visible in 1953.

He went to normal schools and was top of his class in English. He left school at the age of 15 and his apprenticeship to an upholsterer ceased following a difference of opinion with his master. He was at this time quick-tempered and unsociable. 'I would stay at home and read a book rather than go anywhere. I crept into my shell and this had an adverse effect upon me.' He managed to overcome this tendency after treatment by a psychiatrist. He is now a trainee engineer. It was not possible to arrange a formal test but his intelligence is clearly within the normal range. His conversation and attitude to life are introspective, detailed, repetitive, and obsessional.

Although symptoms were clearly present from an early age, and treatment was inadequate at least until the age of 1½ years and probably until the age of 3 or 4 years, his mental development is normal. He shows characteristic obsessional traits.

It has long been recognized that so far as the physical symptoms of the disease are concerned thyroid by mouth is a completely effective substitution therapy. The initial dosage should not be in excess of 1/6 grain a day and this should be increased only gradually over weeks or months to the optimal dosage which probably never exceeds 2 grains a day. Study of the records of the seven children who died at Great Ormond Street between

1917 and 1938 confirms the impression recorded by Pugh (1952), and well documented in the literature that the greatest hazard to the life of the young cretin is an unnecessarily high starting dosage of thyroid or its over-rapid increase. Death was probably attributable to this cause in all seven cases. The effect of treatment upon mental development is less consistent, and the majority of adequately treated cases remain on the borderline of educability. A number are more grossly defective, and only a small minority achieve normal intelligence. The hypothesis that the mental prognosis would be greatly improved if all cases were treated from the earliest possible time at which a clinical diagnosis could be made has never been critically tested, and there is much to suggest that this would not be the case.

Types of Sporadic Cretinism

Until the last few years there had been no prospect of making any progress in splitting sporadic cretinism up into its constituent entities, although it has been clear for many years that it was not a single disease.

Complete agenesis of the thyroid gland was first demonstrated by Curling (1850) and in all the published series this has been the commonest finding. But in roughly 10% of necropsies the gland has been present, and usually enlarged, and the clinical presence of a goitre in a minority of cases has also been remarked. Murray (1900) quotes two series. Fletcher Beach found goitres clinically in seven out of 116 cases, and of 16 of this series which came to necropsy two had large thyroid glands. Byron Bramwell found a thyroid gland in one out of 10 necropsies. Osler (1905) found goitres clinically in seven out of 60 cases.

In the period 1917-1938, seven patients died in The Hospital for Sick Children. Of the six cases which came to necropsy, the thyroid gland was entirely absent in five, and was enlarged in one case.

Pugh (1952) recently analysed the available records of the 21 necropsies done on cases of cretinism in the same hospital between 1860 and mid-1952. The thyroid gland had been reported as 'entirely absent' in 14 cases. Of the remaining seven, it had been 'small' in two, 'normal' in one, and 'enlarged' in four.

The recorded familial incidence is also such as to suggest two distinct diseases, for the familial cases seem to be concentrated in a very small percentage of the families. Murray (1900) refers to two such families: in one of these, four out of 11 members were affected, and in the other, three members were affected.

Until recently these two criteria, upon each of which cretinism could be split into two separate entities, appeared to be unrelated. Stanbury and Hedge (1950) reported a family in which four of seven children were goitrous cretins, and more recently McGirr and Hutchison (1953) have reported radio-iodine studies upon 12 cases of non-endemic goitrous cretinism. Of these 12 cases, four were in one family and two others were closely related. The defect appeared to be one affecting the capacity of the thyroid gland to synthesize thyroxine. Radio-iodine was taken up rapidly, in such a way as to suggest hyperfunction in the gland, and was subsequently found in the blood stream in a protein-bound form, but this could not have been thyroxine as the cases responded normally to thyroid extract given by mouth. Similar results were obtained from radio-iodine studies in Stanbury and Hedge's cases.

These findings appear to link the familial and goitrous cases and to suggest the possibility that there is a form of cretinism due to an enzyme defect of the thyroid gland controlled perhaps by a new mutant dominant gene. Whatever may come of further investigation of this group of cases, the study of radio-iodine uptake by the gland, and of its subsequent distribution and excretion in relation to the clinical findings and response to administered thyroxine opens up new possibilities for the precise definition of all thyroid disorders, including the sub-division of cretinism, and will form an integral part of any future researches in this field.

The Cause of Mental Defects in Athyrea

The failure of thyroid treatment to cure mental retardation was for long held to be due to delay in diagnosis and treatment; this view has come to be largely abandoned on evidence which, though good and abundant, is still circumstantial. For although non-endemic cretinism has been recognized in this country for 80 years, there has been a consistent failure to observe groups of cases in such a way that the problems of management and prognosis could be solved.

The association of mental defect with cretinism can be explained in two ways. Either they are due to separate lesions of common cause—and analogous therefore to component parts of the rubella syndrome—or the mental defect is the result of thyroxine starvation of a potentially normal brain. The idea that mental defect and cretinism might be two separate congenital disorders, of common origin but not causally related to each other, seems to have arisen (Tredgold, 1929) as an attempt to explain the failure of thyroid substitution therapy to achieve

all that was expected of it. No good evidence in favour of this aetiology has been obtained, however, and it seems likely that evidence against it will accrue in the process of classifying the diseases hitherto described together as cretinism. If cretinism and defective development of the brain were unrelated except through common origin it is unlikely that they would co-exist in cases of cretinism due to different pathological causes. If therefore it is shown with the help of radio-tracer studies that mental defect is associated with non-endemic cretinism due to causes other than simple athyrea, it will be highly probable that the cretinism is the cause of the mental defect rather than of common origin with it. Studies of endemic cretinism may also provide evidence on this point. Endemic cretinism is said to be associated with a mental defect more consistent and more severe than that of sporadic cretinism. It is to be hoped therefore that precise studies of the mental prognosis in a series of treated endemic cretins will be made before simple public health measures have eradicated the disease throughout the world.

It seems inherently more probable, and it is a more economical hypothesis, that the mental defect follows thyroxine starvation of the rapidly developing brain ante-natally and in the early months of separate existence.

But even if it could be proved that thyroxine deficiency was the cause of the mental defect it would by no means follow that cases could be diagnosed early enough to remedy the defect in mental development. Knowledge of the age at which foetal thyroid secretion begins, the age at which, if at all, it becomes necessary to ante-natal development, and of the capacity of maternal thyroxine to cross the placental barrier and replace it when deficient, is very limited. The following details are taken from Clement Smith (1945):

> The thyroid is structurally complete at the third to fourth month and colloid is stored at six months. Thyroxine has been identified in the human foetus at the third month and iodine is concentrated in the thyroid gland by the end of the first third of development. There is evidence that the placenta can transmit thyroxine in both directions, but the consistency of this interchange and its quantitative adequacy are not known. It is probably not an unimpeded flow. In the first few days of post-natal life the colloid is depleted and the gland becomes hyperaemic.

Before sure knowledge can be obtained of the exact relationship between cretinism and its facultatively associated mental defect more will have to be learned about the thyroxine requirements of the individual in the few weeks before and after birth.

In cases of congenital athyrea, which form the great majority of cretins, there can be no autochthonous thyroxine in the individual at any time: if, therefore, thyroxine is necessary to brain development at any phase it must in some cases be obtained from another source, for a minority of individuals so afflicted are of normal intelligence. The variability of mental development from case to case could only be accounted for by variations in the adequacy of such alternative supply. The only conceivable alternative sources are placentally transmitted maternal thyroxine ante-natally, and transmission via the milk supply post-natally. The greater severity and consistency of mental defect in endemic cretinism might on this hypothesis be accounted for by the fact that in these cases the maternal thyroid is itself working under difficulties while competing with the foetus for the limited supply of iodine.

This hypothesis assumes a direct dependence of the foetal brain upon thyroxine for certain phases of its development. There is, however, another highly speculative alternative which seems worthy of consideration. An inadequate level of circulating thyroxine stimulates the production of thyrotrophic hormone, whether a thyroid gland is present or not. In cases of cretinism, the hypophysis is hypertrophied (Horsley, 1892). Could it be that this hypertrophy of a single function in early foetal life takes place at the expense of other, and as yet unknown pituitary mechanisms controlling cerebral development?

Conclusions

Sporadic cretinism was recognized in this country towards the end of the nineteenth century, and it was soon shown that thyroid substitution therapy was effective in the control of the physical symptoms of the disease and in securing normal physical development.

The position with regard to mental prognosis is, however, still confused and the field is open for long-term studies upon the effect of the earliest possible diagnosis and treatment.

It has been a consistent finding so far that the ultimate intelligence of adequately treated children varies widely and that the degree of success in this respect shows no positive correlation either with early diagnosis or with the degree of persistence with which treatment has been maintained. There is, on the other hand, some evidence that the mental prognosis is worse in those cases which are diagnosed and treated from the earliest months of infancy. It should be noted that there is one source of confusion in analysing evidence of this kind which is common of the study of a variety of congenital

diseases in which clinical severity varies from case to case. This is that the more severe are likely to be diagnosed earlier in life than milder cases, thus unjustifiably weighting the statistical evidence against the value of early treatment.

It is possible that cases in which mental defect is established by, or shortly after birth, will tend to be diagnosed earlier in life and while the physical symptoms are minimal, merely because the mental retardation itself has brought the child to the notice of the physician.

It is clear that sporadic cretinism is not a single disease. That it consists in not less than two entities is proved by the observation at necropsy that the thyroid gland is present in some cases but not in others. It may be possible to define the pathology of cases in which a gland is present by means of radio-iodine studies.

Under treatment the majority of cases reach the borderline of educability; many are more grossly defective and only a minority achieve normal intelligence. In addition to the mental defect there are often personality defects which may interfere with the social performance of those who, in terms of formal intelligence, are on the borderline of educability.

Initial doses of thyroid should not be more than 1/6 grain daily as most of the mortality appears to be due to an excessive starting dosage, and the optimal dosage, which should seldom exceed 2 grains a day, need not be reached for weeks or months. There is a general agreement that increases in dosage over 2 to 3 grains a day are valueless. It has been shown that $1\frac{1}{2}$ grains of thyroid will replace the normal activity of the thyroid gland in a child of 6, $1\frac{1}{2}$ to 2 grains would, therefore, probably never be too little, and could hardly be too much in the presence of thyroid deficiency because even if there was some residual function in the thyroid gland this would presumably be controlled by normal physiological mechanisms to achieve a satisfactory total level of circulating thyroxine.

There is, on the other hand, good evidence that excessive dosage may interfere with development of the personality and with the most efficient use of what mental equipment is available. If, as is here suggested, the basic intelligence is fixed by the time the case is diagnosed, and perhaps by the time of birth, then no great improvement can be expected from earlier diagnosis, and the prognosis as regards mental development will remain as is recorded in the literature; that is to say, the majority will be in the I.Q. range 70-95, some will be grossly defective, and a very few will be of normal intelligence. This point can only be further clarified by a closer and longer study of a series of earlier treated cases than the literature yet contains.

Summary

It is certain that there is more than one type of non-endemic cretinism, for in a minority of cases the thyroid gland is apparently normal or enlarged. Recent studies suggest that sporadic cretinism without athyrea may be a familial disease. Radiotracer techniques for the study of iodine metabolism offer the hope of further definitions of the two or more diseases which comprise non-endemic cretinism.

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THE ABSORPTION OF SHORT-CHAIN FATS BY PREMATURE INFANTS

BY

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That premature infants commonly exhibit defective fat absorption has been known for many years (Rubner and Langstein, 1915; Muhl, 1923; Tidwell, Holt, Farrow and Neale, 1935). This steatorrhoea is, however, masked and the excess of unabsorbed fat does not separate out in the gross or in microscopically detectable globules.

Efforts to compensate for the caloric deficit caused by this unabsorbed fat have followed several lines, such as low-fat feedings (Gordon and McNamara, 1941), homogenization (Morales, Chung, Lewis, Messina and Holt, 1950b) and emulsifying agents (Snyderman, Morales, Chung, Lewis, Messina and Holt, 1953) to facilitate fat absorption and the use of the more readily assimilable unsaturated fats (Tidwell *et al.*, 1935). The present authors have also shown that increasing the fat intake improved absolute absorption (Morales *et al.*, 1950a) and did not produce deleterious effects.

A further approach to the problem was suggested by the work of Frazer (1946) which indicated that short-chain fats were absorbed through the portal circulation rather than by the lacteals. It seemed possible that the absorption defect in the premature infant might be confined to the lacteal mechanism and that portal absorption would be quite normal. In this event the defect in fat absorption could be overcome simply by feeding short-chain fats.

Observations of this kind were therefore made, using tributyrin and triacetin to replace butter fat in feeds.

Experimental

Subjects. Six premature infants were used in the present study. They varied in weight from 1,350 to 2,010 g. and in age from 5 to 43 days at the beginning of the study.

Feeds. A stock formula consisting of skim milk, dextrimaltose and water was given to all these infants. The fat was weighed just before the feed and fed by gavage. This was washed down by part of the formula. The remainder of the formula was then given by nipple. This method was adopted in order to be certain that each infant received his entire quota of fat. The formula had the following caloric composition: protein 18%, fat 34% and carbohydrates 48%, and was given at the level of 130 calories per kilogram of body weight per day. A standard water-soluble vitamin preparation was continued throughout the period of observation. Corn oil was given for three experimental periods in the form of a proprietary infant food.*

Collection of Faeces. These were collected as described in a previous publication (Morales *et al.*, 1950a).

Experimental Periods. These were of four days' duration in all instances.

Fat Analyses. These were carried out on the faeces using the procedure of Tidwell and Holt (Tidwell and Holt, 1936).

Results

Table 1 shows the fat balances obtained in six infants when tributyrin and triacetin were substituted for butter fat. The superior absorption of tributyrin and triacetin is clearly shown; there was virtually complete absorption of both fats. The absorption of these two triglycerides was also superior to that of corn oil which had previously been shown by one of the present authors (Tidwell *et al.*, 1935) to be better than butter fat.

Clinically, these infants did quite well on the short-chain fat feedings. There were, at no time, any untoward symptoms or signs that could be attributed to these feeds. Their weight gain on these feeds was in every instance better than on the butter-fat feed; it was inferior to that on the corn-oil feed because of the larger caloric value of the latter feeds. The comparative weight gains on these various forms of feed are shown in Table 2.

* Olac, kindly supplied by Mead Johnson & Co.

TABLE 1
FAT BALANCES IN SIX INFANTS

Case	Age (days)	Initial Weight (g.)	Type of Fat	Fat Intake (g./day)	Faecal Fat (g./day)	Fat Retention	
						(g./day)	% Intake Retained
Morrero ..	50	1,890	Tributyrin	10·8	0·08	10·72	99·4
			Butter fat	11·5	6·44	5·06	44·0
			Tributyrin	12·0	0·22	11·78	98·0
Camerero ..	10	1,630	Tributyrin	8·0	0·15	7·85	98·2
			Butter fat	11·5	6·69	4·81	41·9
			Tributyrin	11·5	0·30	11·20	97·3
Ford A	5	1,350	Tributyrin	6·6	0·41	6·19	93·6
			Butter fat	7·2	4·03	3·17	44·0
			Tributyrin	7·9	0·74	7·16	90·8
			Corn oil	8·98	2·0	6·98	77·6
			Triacetin	10·2	0·14	10·06	98·5
			Butter fat	10·1	1·81	8·29	82·0
Ford B	5	1,400	Tributyrin	8·0	0·10	7·90	98·8
			Butter fat	8·4	3·82	4·58	54·5
			Tributyrin	8·7	0·10	8·60	98·9
			Corn oil	10·0	1·27	8·73	87·3
			Triacetin	10·2	0·15	10·05	98·3
			Butter fat	10·9	2·25	7·65	70·3
Feliciano ..	15	2,100	Triacetin	9·9	0·09	9·81	99·3
			Butter fat	10·6	4·35	6·25	58·8
			Triacetin	10·6	0·10	10·50	99·0
			Corn oil	11·8	0·8	11·0	93·2
Robbins ..			Butter fat	8·7	2·86	5·84	67·2
			Triacetin	9·4	0·18	9·22	98·2
			Butter fat	10·1	4·34	6·76	66·8

TABLE 2
WEIGHT CHANGES

Case	Fat	Weight Change (g./day)
Morrero ..	Tributyrin	+28·6
	Butter fat	+18·3
	Tributyrin	+20·0
Camerero ..	Tributyrin	+42·5
	Butter fat	− 3·3
	Tributyrin	+55·0
Ford A	Tributyrin	+25·0
	Butter fat	+17·5
	Tributyrin	+20·0
	Corn oil	+32·8
	Triacetin	+15·0
	Butter fat	+ 6·7
Ford B	Tributyrin	+24·3
	Butter fat	+ 3·3
	Tributyrin	+23·4
	Corn oil	+38·4
	Triacetin	+20
	Butter fat	+16
Feliciano ..	Triacetin	+23·4
	Butter fat	− 1·7
	Triacetin	+34·2
	Corn oil	+31·6
Robbins ..	Butter fat	+18·4
	Triacetin	+35·7
	Butter fat	+28
Average of 8 periods on tributyrin		+29·9
Average of 4 periods on triacetin		+28·3
Average of 3 periods on corn oil		+34·3
Average of 9 periods on butter fat		+11·5

Comment

The above studies indicate that the defect of fat absorption in premature infants can be overcome by the use of short-chain fats such as triacetin and tributyrin. This finding is a matter of scientific interest, suggesting as it does that the portal mechanism of fat absorption is unimpaired and that the lacteal mechanism alone is affected. As a matter of practical therapy, however, the substitution of the short-chain fats for butter appears to have little or no advantage from the point of view of supplying calories, since shortening the fatty acid chain involves a corresponding loss in energy yield. Tributyrin yields only 6·7 calories per gram and triacetin offers no appreciable caloric advantage over protein or carbohydrate.

Summary

Premature infants will absorb short-chain fats without difficulty, presumably because the portal absorption mechanism is unimpaired. The superior absorption of these fats is counterbalanced by their inferior caloric yield.

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A STUDY OF CEREBRAL PALSY IN THE CHILDHOOD POPULATION OF EDINBURGH

BY

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There is increasing interest in the needs of children suffering from cerebral palsy for special education and medical treatment and for measures to render more of them employable. Many schemes to provide facilities for education and employment are being planned, but there are only a few scattered systematic surveys of the incidence of cerebral palsy in childhood, and so the size of the problem is largely unknown. This article presents the results of a recent investigation which was designed to assess the incidence of cerebral palsy in children resident in Edinburgh.

The Plan of the Survey

The survey was confined to children born in the years 1938 to 1952 inclusive who lived within the boundaries of the City of Edinburgh. Since the population of this age group in the city was more than 100,000 it was clearly impossible to examine every child individually. On the other hand, the medical services of the city work in close liaison and the school medical and public health authorities are highly developed. Due largely to the propaganda of the Scottish Council for the Care of Spastics there is a great awareness of, and interest in, the problems of the child with cerebral palsy among doctors, teachers and medical auxiliaries. Therefore children in whom cerebral palsy was suspected tended to be over-examined rather than neglected. Thus in many ways Edinburgh was an ideal city in which to obtain information about children with cerebral palsy and make a survey of its incidence.

The Methods of the Survey

Details of the children who might be suffering from cerebral palsy were obtained in three ways in the first part of the survey. First, large numbers of case notes and reports from clinicians were examined, and all cases in which cerebral palsy was suspected were noted. Secondly, all patients whose records showed that they suffered from conditions known to be associated commonly with cerebral palsy were listed. These included children with mental defect with clumsiness, epilepsy, hydrocephalus, talipes equinovarus and arthrogryposis. At the same time all patients who gave histories of having suffered from conditions likely to lead to cerebral palsy were noted. These included patients with apparent birth injury, rhesus incompatibility, meningitis, encephalitis, cerebral thrombophlebitis and head injury. Thirdly, inspections and brief examinations were made of groups of children in whom a high incidence of cerebral palsy might be expected. Thus large numbers were examined in schools for the physically and mentally handicapped, in clinics for the premature infant and in institutions for the mentally defective.

Sources of Ascertainment

The sources of information about possible and probable cases of cerebral palsy were very numerous and overlapped considerably. The more important sources of information will be mentioned. Access was given to the case notes of the officers of the School Medical Service, who were uniformly most helpful in providing information and facilities for the examination of their patients. In all, over 6,000 case notes were examined in various schools and over 400 patients seen in schools by arrangement with school medical officers. Information about educational difficulties and progress was obtained in as many cases as possible from teachers.

Fifty-five private schools were contacted and information sought about any children with disabilities suggestive of cerebral palsy. Replies were received from 53 of the private schools.

The officers of the Maternity and Child Welfare Service were most helpful in giving information about children they felt might be suffering from cerebral palsy, and access was given to case notes and patients in their clinics. The results of the routine health visiting of the department were also made available to the investigation. The Public Health

Department physicians and surgeons provided information about patients with cerebral palsy visiting their clinics.

All hospitals in Edinburgh concerned with the diagnosis and treatment of children's diseases, of whatever type, and maternity hospitals in the city were contacted and in each instance ready access to case notes and patients was granted. Medical, nursing and auxiliary staff were questioned about possible cases and approximately 2,500 case notes dating back to 1940 were examined. Out-patient staffs and case notes were consulted as well as in-patient notes and staffs. Many consultants, physicians and surgeons gave access to their private patients and went to considerable trouble to arrange for the investigator to examine these children.

The Scottish Council for the Care of Spastics gave free access to their patients and records and much valuable information was obtained from the highly trained members of their staff.

The response of general practitioners to the request for information about their patients was disappointing. It was intended to contact all general practitioners in Edinburgh by letter requesting details of children who, they thought, might be suffering from cerebral palsy. As a first step, 25 practitioners were circularized and asked for information. They were known at that stage of the investigation to have at least 28 patients with cerebral palsy in their practices, but only two names were obtained and only one of these was unknown to the survey. General practitioners were not hereafter contacted specifically to obtain information about the numbers of patients with cerebral palsy in their practices, but whenever permission was sought to examine known cases doctors were always asked for details of any other cases known to them.

Other research projects amongst children in Edinburgh provided a number of cases of cerebral palsy. These included investigations of children with mental defect, of children who had suffered from meningitis, of infants with retrolental fibroplasia, the prematurely born and children who had suffered cerebral birth injury.

A few additional cases were reported by district nurses, infant clinics, speech therapists, child guidance clinics and teachers.

Direct Ascertainment of Cases of Cerebral Palsy

Direct ascertainment of children with cerebral palsy was carried out in groups of children in whom a high incidence of cerebral palsy was to be expected. The usual procedure was to watch the children at play for as long as possible and then when they attempted to sit still. Those in whom cerebral palsy was suspected on the basis of these inspections were examined. After a few months, during which experience was gained, it was found that quite as many cases of cerebral palsy were noted using this method as were discovered by detailed examination of all the children in a group.

Approximately 4,000 children were inspected in ordinary schools, special schools, nurseries, institutions for the mentally defective and infant clinics.

Results of Preliminary Ascertainment

As a result of the first part of the investigation 484 children were classified as possible cases of cerebral palsy and 165 as probable cases. Probable cases were those children who had been diagnosed as suffering from cerebral palsy by other observers or were felt to suffer from the condition as a result of the inspections of the investigator. Possible cases were those children in whom a diagnosis of cerebral palsy could not be excluded on the basis of information provided in case notes which had been inspected, or who had suffered from some condition known to lead to, or be associated with, cerebral palsy in a proportion of patients. It was felt to be desirable to examine and obtain some details of the history of the development and course of the condition in all the children in both the possible and probable categories.

Probable and Possible Cases. All the 165 children who were considered to be probable cases of cerebral palsy were examined with the exception of two for whom permission for examination was refused. In four cases a detailed history could not be obtained.

Of the 484 possible cases of cerebral palsy all but 85 were examined. Of the latter it was possible to obtain reliable information of recent medical examinations in 52 so that the presence of cerebral palsy could be excluded. In the remaining 33 patients it was impossible to obtain such information and it was not found possible to examine them. The 399 patients who were examined were usually seen briefly at the time of the routine school medical examination for the first time and then examined in more detail later if the presence of cerebral palsy was confirmed.

The history was obtained from the mother whenever possible and was supplemented by details of hospital admissions and clinic visits, maternity hospital and infant clinic notes and the recollections of other relatives.

In practically all the patients in the series physical examinations were performed on more than one occasion, preferably in different surroundings and preferably at intervals of a few months. Full

clinical examinations were supplemented by special examinations, blood investigations, radiographs, intelligence tests and electroencephalograms in relatively few cases, but frequently these were available as a result of previous hospital admissions or school testing.

Classification of Types of Cerebral Palsy

The classification by neurological syndromes which was used during the survey is shown in Table 1. It will be observed that it is not based on single clinical features, such as alteration of muscle tone, as have many recent classifications (Phelps, 1940; Hellebrandt, 1950-51). By laying stress on single clinical features of cerebral palsy great confusion has been caused. Too close adherence to rigid classification on this basis has led to verbal absurdities like categories of 'aspastic spastics' and nosological confusions like 'cerebellar release athetosis'. Cases of hemiplegia may be found under headings of 'rigidity' and 'spasticity', though the only difference in clinical features is that contracture is more marked in the former group. It is noteworthy that, when authors using some of these complex modern classifications wish to compare series of patients suffering from different forms of palsy, they immediately resort to grouping paraplegic, triplegic and tetraplegic cases together and distinguish them from the hemiplegic forms. Yet in their classifications all these types of cerebral palsy are found together in categories of 'rigidity' and 'spasticity'. To eliminate such confusions it is desirable to resort to the earlier, well tried types of classification by neurological syndromes.

TABLE 1
CLASSIFICATION OF CEREBRAL PALSY IN CHILDHOOD

Neurological Diagnosis	Extent	Severity
Hemiplegia	Right / Left	Mild / Moderately severe / Severe
Double hemiplegia		Mild / Moderately severe / Severe
Diplegia: Hypotonic, Dystonic, Rigid or spastic	Paraplegic / Triplegic / Tetraplegic	Mild / Moderately severe / Severe
Ataxic diplegia: Hypotonic, Spastic	Paraplegic / Triplegic / Tetraplegic	Mild / Moderately severe / Severe
Ataxia: Cerebellar, Vestibular	Predominantly Unilateral / Bilateral	Mild / Moderately severe / Severe
Dyskinesia: Dystonic, Choreoid, Athetoid, Tension, Tremor	Monoplegic / Hemiplegic / Triplegic / Tetraplegic	Mild / Moderately severe / Severe

The present classification is based on that suggested by Freud (1893, 1897), shown in Table 2, with some modifications rendered necessary by the widened scope of the term 'cerebral palsy' since his time, and by advances made in the knowledge of the nature of some forms of the condition. Freud included cases showing involuntary movements as the predominant clinical findings in the category of diplegia, though with some misgivings. In the present classification cases showing involuntary movements as the presenting symptom have been grouped under the heading of dyskinesia, and classified as suggested by Perlstein (1952). Largely to achieve some uniformity with contemporary American classification Freud included cases of bilateral hemiplegia under the heading of 'diplegia' (Lovett, 1888; Osler, 1889). In the present classification these cases have been placed in a separate category. In accordance with modern practice the category of ataxia has been added.

TABLE 2
CEREBRAL PALSY IN CHILDHOOD AS CLASSIFIED BY FREUD (1897)

Unilateral disorders	Hemiplegia: right / left
Bilateral disorders	Diplegia: Paraplegic rigidity; Generalized rigidity; Bilateral hemiplegia; Choreoathetosis
Possibly other groups	

By 'diplegia' is understood a condition of more or less symmetrical paresis of cerebral origin more severe in the lower limbs than the upper and dating from birth or shortly afterwards. It will be observed that separate categories have been made for patients showing diplegia without ataxia and those showing diplegia associated with cerebellar ataxia. The aetiologies of these disorders differ, and the course and findings on examination are dissimilar.

A high proportion of patients suffering from diplegia without ataxia are born prematurely (40% in the present series). Many show associated mental defect, epilepsy and strabismus. There is a constant pattern of development of the paresis, inadequately described in modern textbooks, in which only the final stage of diplegia, characterized by spasticity and contractures, is mentioned. In at least half the patients suffering from diplegia without

ataxia three stages may be distinguished in the development of the final clinical picture.

For a period after birth the child may be thought to be normal, but in a proportion of patients the parents note that the baby is floppy and flaccid on handling and shows a relative poverty of movement when compared with others of the same age. On examination at this stage these patients show generalized hypotonia without any other apparent neurological abnormality in most cases. The stage of hypotonia persists for between six weeks and five months in the majority of those showing it and is succeeded by the stage of dystonia.

The stage of dystonia is first manifested by sudden generalized dystonic movements involving the trunk and limbs and precipitated by changes in the position of the child, especially extension of the head relative to the trunk. The involuntary movement consists of a sudden extension of the head and trunk, extension of the hips and knees, and plantar flexion of the feet. The upper limbs are adducted and somewhat internally rotated at the shoulders and extended at the elbows. The wrists and fingers are semiflexed and the forearms are pronated. On examination when in this position marked rigidity is found in all the muscles of the trunk and limbs. The child maintains the position of extension of the trunk and limbs for a few seconds during which time consciousness may seem slightly impaired, though it is never lost, and then the muscles again relax. Initially the sudden dystonic attacks occur relatively infrequently and only when the child's position is suddenly or grossly altered, but over a period of two or three weeks the attacks become more frequent and more readily precipitated. The generalized attacks seldom persist for less than three weeks or for longer than six months. Towards the end of the dystonic stage they become less frequent and more difficult to produce. At about the time the child is able to hold the head up steadily the generalized dystonic attacks cease in most patients and simultaneously rigidity of the limbs first becomes apparent, marking the end of the dystonic and the beginning of the rigid or spastic stage of diplegia. With the cessation of the generalized attacks the child tends to show an increase in the range and control of voluntary movements and begins to reach for objects. It is observed at this stage that though voluntary movements or changes in position no longer result in involuntary extension of the trunk, the limbs continue to assume positions similar to those noted during the earlier dystonic attacks. Rigidity is usually first evident in the thighs. It increases in a matter of a few weeks and at the same time spreads to involve the distal parts of the lower limbs and, in all but paraplegic patients, the upper limbs. The rigidity tends to result in the limbs being held in positions of predominant extension as in the earlier dystonic attacks, and these positions are accentuated by voluntary movements or passive changes in position. The phase of rigidity with predominantly extensor associated movements usually persists until the patient is able to sit without support with the knees flexed and handle objects. Commonly this is shortly before the age of 1 year in patients who are not mentally defective. The phase of rigidity merges imperceptibly into the phase of spasticity at about this stage of the child's development. The tendon jerks become increased instead of being difficult to elicit and stretch responses appear in the muscles. The Babinski responses become positive. Instead of extensor associated movements predominantly flexor associated movements accompany voluntary movements of the limbs. When spasticity is present, contracture of the limbs in flexion almost invariably follows unless the child is treated, and the final stage of diplegia is reached.

The stages which are apparent in the development of diplegic paresis appear to be of more significance than mere indications of the diagnosis. In severe cases the stage of rigidity or spasticity may never be reached and dystonic attacks may persist throughout life whenever the child attempts voluntary movement involving changes in posture. The child's neuromuscular development may be regarded as having been arrested at the relatively primitive stage of dystonia. On the other hand, the infant in whom spasticity with flexor associated movements is evident, shows neuromuscular development which may be regarded as being more mature. The child will be able to achieve more adequate motor control than will the child with persistent dystonia provided contracture is prevented. One remnant of the generalized dystonic attack persists quite commonly in patients showing predominant rigidity in the muscles and they may be regarded as being in an early phase of the rigid or spastic stage of diplegia. It is found that when these children attempt to walk a sudden extension of the neck, trunk and lower limbs ensues, a phenomenon known to physiotherapists as extensor thrust. By classifying the patient with diplegia according to the stage of the development of his condition, a clear indication is given of the maturity of his neuromuscular control.

Patients with diplegia associated with cerebellar ataxia show only two of the stages found in cases of diplegia without ataxia. Initially most of the children are hypotonic, but the majority show increasing spasticity of the limbs, more marked in

the legs than the arms from the age of 9 or 10 months. Attacks of dystonia are never found and the predominant associated movements are flexor not extensor. The increase of tone is never rigid, but is spastic and the tendon jerks are invariably much increased. The Babinski responses are always bilaterally positive. A high proportion of these patients and their relatives are mentally defective, and in three females of the 13 patients with diplegia and cerebellar ataxia in the present series, there was a similar condition in the mother or in female siblings. On examination, in addition to the findings of paresis of the limbs, with a spastic increase of tone, there is cerebellar ataxia, which may be predominantly unilateral or bilateral.

Cases which could not be conveniently classified in any of the foregoing categories were placed in the category of 'other'. They included only two patients in the present series, one with arthrogryposis and cerebral palsy confined to the cranial nerves and one with post-encephalitic Parkinsonism.

The Extent and Severity of the Palsy

The number of limbs so severely involved neurologically that their full normal functions were impaired is stated for each category of cerebral palsy. Limbs involved neurologically but not affected severely enough to limit their functions were classified as normal limbs. Thus the extent of the palsy which is stated is the extent of functional impairment and not of neurological involvement. It was rare, for example, to find paraplegic patients who did not show some evidence of slight affection of the upper limbs. The side affected by hemiplegia was stated in every case.

The severity of the palsy was somewhat arbitrarily decided on the basis of different criteria for each form of cerebral palsy. Thus mild cases of hemiplegia were those in which the affected arm was capable of being used, if somewhat clumsily. Moderately severe cases were those in which the arm was useful only as an assistant to the unaffected arm, and severe cases were those in which there was very little if any functional use in the affected upper limb. Mild cases of diplegia and diplegia with ataxia were those in which the gait was clumsy but not grossly impaired. Moderately severe cases were those in which walking without support was possible but the gait was abnormal and activities were limited because of this. Severe cases were those in which walking without support was impossible or possible for only very limited distances. Mild cases of ataxia and dyskinesia were those in which the child's activities were not limited, moderately severe cases were those in which some ordinary activities, such as dressing and feeding, were possible only with difficulty. Severe cases were those in which all normal activities were severely handicapped. Bilateral hemiplegia was always a relatively severe condition. Moderately severe cases were those which could stand or walk without support. Severe cases were those in which walking was impossible, and, since the upper limbs were more handicapped than the lower limbs, the former were generally almost functionless.

Incidence of Cerebral Palsy by Year of Birth

In Table 3 is shown the incidence of cerebral palsy in Edinburgh children born between 1938 and 1952 as ascertained during the survey. It will be seen

TABLE 3
INCIDENCE OF CEREBRAL PALSY BY YEAR OF BIRTH IN EDINBURGH*

Year of Birth	Population	Number of Patients			Incidence per 1,000 in 3-year Periods		
		Hemiplegia	Diplegia	All Types	Hemiplegia	Diplegia	All Types
1938	6,749	10	3	17	0·819	0·563	1·945
1939	6,574	3	8	13			
1940	6,209	3	0	8			
1941	6,099	4	2	10	0·631	0·578	1·839
1942	6,388	4	4	13			
1943	6,538	4	5	12			
1944	6,533	7	11	24	0·930	1·028	2·546
1945	5,993	4	3	9			
1946	7,902	8	7	19			
1947	8,900	8	7	21	0·871	0·996	2·448
1948	7,700	6	4	14			
1949	7,500	7	13	24			
1950	7,200	5	3	11	0·330	0·566	1·132
1951	7,100	1	6	8			
1952	6,900	1	3	5			
1938–52	104,285	75	79	208	0·719	0·757	1·991

* Based on figures obtained from the Education Authority and estimates of the Registrar-General.

that for the two three-year periods from 1944 to 1949 the incidence of cerebral palsy is approximately 2·5 cases per 1,000 of the population. For the periods before 1944 and after 1949 the figures for incidence are lower.

The apparently lower incidence of cerebral palsy in children born between 1950 and 1952 is partly due to there being a smaller proportion of acquired cases of cerebral palsy than in those born between 1943 and 1949. Though the majority of cases of acquired cerebral palsy occur before the age of 3, a few occur after this age, and clearly a number of children in the group born between 1950 and 1952 have yet to develop the condition. The important cause, however, of the smaller number of patients found among children born in this period compared to those born in earlier years is defective ascertainment. This is true for all the categories of the condition and for congenital as well as for acquired cases.

The reasons for defective ascertainment of patients in the younger age group are of some importance. In a large proportion of patients the early manifestations of the disorder had been misinterpreted or ignored by the doctor to whom the mother took the child. Thus in the 79 cases of diplegia in the series, 64 had symptoms before the age of 18 months. In 58 cases the symptoms resulted in the child being taken to the doctor before this age. Yet the diagnosis of some form of cerebral palsy was made in only 18 cases and the majority of patients had to wait for between 18 months and two years before diagnosis and treatment were undertaken. A delay of this duration resulting in children appearing for treatment only at the age of 3 years or more means that many have reached the stage of contracture before anything is done to limit the effects of the condition. Because the diagnosis of many patients with cerebral palsy born between 1950 and 1952 was unknown to doctors and the patients had not reached clinics or treatment centres, they were not ascertained during the survey.

The apparently lower incidence of cerebral palsy in children born between 1938 and 1943 than in those born between 1944 and 1949 appears to be due to a number of factors. It was difficult to discover why ascertainment should have been more defective for this age period than for those born in the later period. The same sources of information were available and the numbers of routine medical examinations in schools and clinics was greater in the older groups than in the younger. It might have been expected that ascertainment would be more, not less, effective in the older children. It seemed likely that the apparently lower incidence of cerebral palsy in those born between 1938 and 1943 compared with that of those born between 1944 and 1949 was either a true reflexion of a difference in the numbers of patients developing the condition or of the proportion of patients surviving in spite of it.

The death rate in children suffering from cerebral palsy is unknown, though various estimates based on unpublished or inadequate evidence have been made. It seems probable, however, that the commonest cause of death among children suffering from cerebral palsy is infection, especially of the respiratory tract in those with bulbar involvement complicating severe bilateral affection of the limbs. Since the advent of antibiotics these infections can more frequently be controlled and a higher proportion of severely affected children with cerebral palsy may be expected to survive. In the present series there is, in fact, a higher proportion of severe forms of the condition, especially diplegia of tetraplegic distribution and bilateral hemiplegia, among children born between 1944 and 1949 than in those born between 1938 and 1943.

In addition to the increase in the number of patients with cerebral palsy born in 1944-49 compared with those born in 1938-43 due to the lower death rate in the later period, there is an increase in the numbers suffering from the condition as a result of certain aetiological factors. The increase is most marked in cases of acquired ataxia and hemiplegia. The numbers suffering from the latter who were born in the periods 1938-43 and 1944-52 are shown in Table 4. It will be observed that there is a significantly higher proportion of patients in the second group who suffered from acquired hemiplegia, the result of the cerebral complications of acute infections. It seems probable that the effect of antibiotic therapy has been to lower the mortality from these acute infections and that a higher proportion of patients suffering from them are surviving to show the effects of cerebral damage. Similarly, there appears to be an increase in the numbers of

TABLE 4

RELATIVE NUMBERS OF CASES OF ACQUIRED HEMIPLEGIA IN 1938-43 AND 1944-52 COMPARED

Period	No. of Cases of Hemiplegia	No. of Cases of Acquired Hemiplegia	No. of Cases of Acquired Hemiplegia Treated with Penicillin
1938–43	28	8	2*
1944–52	47	25	17
1938–52	75	33	19

* Both developed infections which were treated with penicillin after 1943.

patients born in the period 1944-49 compared with those born in 1938-43 who show ataxia as a result of tuberculous and septic meningitis.

It is more difficult to assess the effects on the incidence of cerebral palsy of the improvements in obstetric and infant care which have taken place since 1938. Between 1938 and 1952 the infant mortality in Edinburgh was halved. Much of this improvement was due to a reduction in the number of infants dying from infections, but the mortality from other conditions was also reduced. Unfortunately the extent of the reductions in the death rate during the past 15 years is unknown for patients with cerebral birth injury, rhesus incompatibility, and other disorders likely to result in cerebral palsy. Nor can the relative importance of these disorders in the aetiology of various forms of cerebral palsy be established in many instances. There does seem to have been an increase in the proportion of prematurely born infants surviving in the past 15 years, indicated in one Edinburgh hospital by a 39% reduction in the neonatal mortality in infants with birth weights between 3 and 5½ lb. It has been estimated that the incidence of diplegia in prematurely born children who survive is approximately 1%, and a large proportion of these patients give a history of neonatal asphyxia, pulmonary atelectasis and respiratory infections (Ingram and Kerr, 1954). Clearly, if an increasing number of premature infants survive, especially of those suffering from these complications, an increase in the incidence of diplegia must be expected. When the numbers of patients with diplegia born in the periods 1938-43 and 1944-49 are compared, it is found that the incidence of diplegia is increased in those delivered in the later period and that a higher proportion were premature than in the earlier (Table 5).

TABLE 5

NOS. OF DIPLEGIC PATIENTS AND OF PREMATURELY BORN DIPLEGIC PATIENTS ASCERTAINED IN EDINBURGH BORN IN THE YEARS 1938–43 AND 1944–49

Period of Birth	No. of Diplegic Patients	No. of Diplegic Patients Born Prematurely
1938–43	22	5
1944–49	45	19

It seems probable that there has been some increase in the numbers of infants surviving the effects of rhesus incompatibility and cerebral birth injury in the past 15 years, but the extent of the decrease in mortality and its effects on the incidence of cerebral palsy, and particularly of congenital hemiplegia and dyskinesia, cannot be estimated.

If the incidence of prematurely born diplegic patients, the incidence of acquired hemiplegia and the incidence of severe bilateral forms of cerebral palsy had been as high in children born between 1938 and 1943 as it was between 1944 and 1949 the figures for the total incidence of cerebral palsy in these periods would have been very similar. It seems probable, therefore, that the apparent increase in the incidence of cerebral palsy since the period 1938 to 1943 is due largely to the widespread use of antibiotics and to improved obstetric and infant care.

Comparison of Incidence of Cerebral Palsy in Present Survey and with Other Surveys

An attempt has been made to compare the incidence of cerebral palsy found during the present survey with the figures obtained during other special investigations. Some comparable figures are shown in Table 6. It will be seen that estimates of the incidence of the condition in children of school age vary between 1·9 and 2·4 cases per 1,000 of the population. A figure of between 2 and 2·5 cases per 1,000 of the school population is probably a fair estimate of the incidence of significant handicaps as a result of cerebral palsy in urban areas.

TABLE 6

INCIDENCE OF CEREBRAL PALSY IN CHILDREN OF SCHOOL AGE IN VARIOUS URBAN AREAS OF GREAT BRITAIN

Authority	Town	Incidence of Cerebral Palsy per 1,000
Selected urban areas		
British Council for the Welfare of Spastics (1948)	Wallasey	2·4
	Norwich	2·0
	Salford	2·0
	Oldham	1·9
Cohen (1954)	Sheffield	1·9
Smallwood (1953)	Bristol	2·0
This survey (1954)	Edinburgh	2·3

During the survey records were kept in every case of the authorities who were aware of the existence of each patient with cerebral palsy (Table 7). It was hoped to compare roughly the incidence figures of other authors whose sources of ascertainment were more limited than in the present survey. It will be observed that if only the school medical service, the public health authorities and general practitioners had been contacted, the incidence of cerebral palsy would have been approximately 1 per 1,000 of the population under the age of 15 years. With cases known to hospitals added the incidence becomes

TABLE 7

SOURCES OF ASCERTAINMENT IN 208 PATIENTS WITH CEREBRAL PALSY IN EDINBURGH

Authority	Nos. of Patients	Cumulative Totals	Incidence per 1,000
School medical service and school for spastics ..	97		
Public Health Department ..	16		
General practitioners ..	1		
Total known to authorities before present survey ..		114	1·094
Hospitals	52	156	1·59
Institutions for the mentally defective	8		
Personal cases	34		
Grand total	208		1·991

1·59. These figures may be compared with the figures of a number of recent surveys shown in Table 8. On the basis of these figures it seems unlikely that the incidence of cerebral palsy varies greatly in different large towns though, necessarily, this conclusion must be regarded as somewhat tentative.

Comparison of Proportional Distribution of Forms of Cerebral Palsy in Different Surveys

It is rather difficult to compare the incidence of the different forms of cerebral palsy in different surveys owing to the wide variations in terminology used and to the different types of classifications which are found. In Table 9 an attempt has been made to compare some of the larger recent series of cases with those found during the present survey. Owing to the inadequate data available the reclassification of cases in other surveys is somewhat speculative.

TABLE 8

INCIDENCE OF CEREBRAL PALSY IN SCHOOL CHILDREN ASCERTAINED AS A RESULT OF LOCAL AUTHORITY RETURNS AND RECENT SURVEYS

Author	Source of Data	Place	Incidence per 1,000
British Council for the Welfare of Spastics (1948) ..	Local authorities	England	1·0
Asher and Schonell (1950)	School Medical and Public Health Authorities and general practitioners	Birmingham	1·0
Dunsdon (1952) ..	Local authorities	Various	1·3
Holoran (1952) ..	School Medical and Public Health Authorities, some hospitals	Leeds	1·6

There is a considerable difference in the proportion of patients suffering from the various forms of cerebral palsy in the surveys. In general, the series based on the examination of candidates for special schools for children with a physical handicap or cerebral palsy show a higher proportion of patients with dyskinesia and a lower proportion of those with hemiplegia. The latter can more frequently manage in normal schools, whereas the former, though the majority of them are relatively intelligent, require special educational provision. Thus Evans's (1948) and Dunsdon's special school candidates show a smaller number with hemiplegia than are found in such surveys as Dunsdon's regional survey, the survey of Asher and Schonell (1950), or the present series. The lower figure obtained for the incidence of dyskinesia in the present series is also partly due to the fact that patients showing the dystonic stage

TABLE 9

PROPORTIONAL DISTRIBUTION OF VARIOUS TYPES OF CEREBRAL PALSY IN RECENT SURVEYS

	This Survey	Asher and Schonell	Evans	Hellebrandt	Dunsdon	
Year	1953	1950	1948	1950	1952	
No. of patients	208	349	112	531	780	
					Special Schools	Selected Areas
Hemiplegia	36·05%	29%	9%	24%	13%	35·3%
Diplegia	(37·95%)	—	—	—	—	—
Type not stated	—	0·6%	2%	7%	—	—
Paraplegia	13·93%	26%		10%	26%	25·5%
Triplegia	11·06%	5%		4%		
Tetraplegia	12·96%		42%			
Bilateral hemiplegia	3·86%	22%		19%	37%	19·6%
Diplegia and ataxia	5·78%	—	—	—	—	—
Ataxia	7·23%	1%	3%	8%	—	—
Dyskinesia	8·18%	10%	40%	27%	13%	7·8%
Other	0·95%	0·3%	—	1%		
Mixed forms	—	6·0%	4·0%	—	11%	11·8%
	100%	99·9%	100%	100%	100%	100%

of diplegia or rigidity with some dystonic manifestations have been classified as diplegia and not as cases of dyskinesia.

It will be noted that the figures quoted for the incidence of ataxia in the present series and in that of Hellebrandt (1950) derived from a specialized cerebral palsy clinic are higher than those of the other series. This is probably due to the fact that children with quite severe cerebellar or vestibular deficit may compensate to a remarkable extent by using the eyes. In many of these patients the Romberg test is negative and very careful examination is necessary to demonstrate even moderately severe ataxia.

It is interesting that the proportional distribution of patients in the other categories of cerebral palsy in this series and in the regional surveys of Asher and Schonell and Dunsdon are broadly comparable.

Sex Distribution of Cases of Cerebral Palsy

In this series, 60·5% of the patients were males and 39·5% females. This distribution is similar to that reported in a number of other recent regional surveys (Asher and Schonell, 1950; British Council for the Welfare of Spastics, 1948). In other surveys a more equal distribution is reported (Cohen, 1954).

In the present series females outnumber males in two forms of cerebral palsy only, bilateral hemiplegia and dyskinesia. The higher proportion of males in the groups of hemiplegic patients was especially marked.

The Severity of the Palsy

In Tables 10 and 11 is shown the distribution of cases by their severity and the numbers of limbs involved. By 'normally useful upper limb' is implied a limb which can be used for normal activities, such as dressing and feeding without gross clumsiness being evident, whether neurological involvement is present or not.

It will be seen that 52 of the 208 patients (25%) were classified as slightly handicapped by cerebral palsy, 80 children (approximately 38%) as moderately severely handicapped and 37% as severely handicapped. Apart from those suffering from hemiplegia severely handicapped patients usually needed assistance in looking after themselves and were unsuitable for employment in present conditions. In patients classified as being moderately severely affected, the possession of one functionally normal upper limb was of crucial importance in deciding if a child required special help in looking after himself or not.

TABLE 10

SEVERITY OF CEREBRAL PALSY IN 208 PATIENTS

Type of Palsy	No. of Mild Cases	Moderately Severe	Severe	Totals
Hemiplegia	27	26	22	75
Diplegia	13	35	31	79
Diplegia and ataxia	4	4	4	12
Ataxia	4	8	3	15
Dyskinesia	4	6	7	17
Bilateral hemiplegia	0	0	8	8
Other	0	0	1	2
Totals	52 (25%)	80 (38%)	76 (37%)	208 (100%)

TABLE 11

EXTENT OF CEREBRAL PALSY IN 208 PATIENTS

Type of Palsy	Two Useful Upper Limbs	One Useful Upper Limb	No Useful Upper Limb	Totals
Hemiplegia	27	48	0	75
Diplegia	33	19	27	79
Diplegia with ataxia	4	6	2	12
Ataxia	15	0	0	15
Dyskinesia	3	3	11	17
Bilateral hemiplegia	0	0	8	8
Other	1	0	1	2
Totals	83 (40%)	76 (37%)	49 (23%)	208 (100%)

Associated Manifestations of Cerebral Palsy

If paresis of the limbs was the only manifestation of cerebral palsy the vast majority of patients would be educable. It is because of the associated effects of the condition, in particular, intellectual impairment, epilepsy, speech defects, visual abnormality and specific learning difficulties, that the majority of patients need special educational help. In Table 14 some of the more important handicaps found in the series of 208 patients with cerebral palsy are recorded.

Intellectual Impairment in Patients with Cerebral Palsy

Routine intelligence tests were not performed on all the patients examined during the survey, but intelligence quotients were obtained for most of those of school age from schools, hospitals and child-guidance departments (Table 12). Since the estimates were obtained as a result of different tests, in the hands of different testers in differing circumstances, too much reliance cannot be placed on the results quoted. However, they are comparable to the more accurate and better controlled results obtained by other surveys (Table 13).

The majority of the children with cerebral palsy in the present series were of subnormal intelligence. Approximately 44% of the tested patients had

TABLE 12

INTELLIGENCE QUOTIENTS OF 208 PATIENTS WITH CEREBRAL PALSY

Intelligence Quotient	Over 115	100–114	85–99	70–84	55–69	Under 55	Untested	Totals
Hemiplegia								
Mild	1	2	4	4	8	5	3	
Moderately severe	2	4	2	4	7	4	3	
Severe	0	4	4	9	2	2	1	
Total hemiplegia	3	10	10	17	17	11	7	75
Diplegia								
Paraplegic	1	5	4	6	7	1	5	
Triplegic	2	2	0	5	3	3	8	
Tetraplegic	0	0	2	4	3	11	7	
Total diplegia	3	7	6	15	13	15	20	79
Diplegia with ataxia	0	2	3	1	1	2	3	12
Ataxia	0	1	3	6	3	0	2	15
Dyskinesia	1	2	2	4	2	1	5	17
Bilateral hemiplegia	0	0	0	0	0	8	0	8
Other	1	0	0	0	1	0	0	2
Totals	8	22	24	43	37	37	37	208
Percentage distribution	3·8	10·6	11·5	20·7	17·8	17·8	17·8	100
Percentage distribution	4·9	12·8	14·3	24·2	21·9	21·9	—	100

TABLE 13

PERCENTAGE DISTRIBUTION OF INTELLIGENCE QUOTIENTS IN THIS SURVEY COMPARED WITH OTHER RECENT INVESTIGATIONS AND A GROUP OF UNAFFECTED SCOTTISH CHILDREN

Intelligence Quotients	130 or More	115 to 129	100 to 114	85 to 99	70 to 84	55 to 69	Under 55	
Dunsdon (1952)	0·5	2	6·2	15·5	17·2	23·6	35	
This survey	4·9		12·8	14·3	24·2	21·9	21·9	
	130 or More	110 to 129	90 to 109	70 to 89	50 to 69	25 to 49	Under 25	Untestable
Asher and Schonell (1950)	0·6	3·4	20·1	26·8	22·9	10·7	11·6	3·9
Holoran (1952)	—	2·8	22·0	36·2	21·3	8·5	3·5	5·7
Unaffected children (Macmeeken, 1939)	4·7	21·2	48·6	24·3		1·3		

intelligence quotients of 69 or less. They were, therefore, in need of special educational provision whatever the severity of their palsy. Fifty-four of the patients, or 32% of those tested, had intelligence quotients of 85 or more and may, charitably, in some cases, be regarded as of normal intelligence.

Incidence of Epilepsy

In Table 15 are shown the numbers of patients who suffered from epileptic attacks of various types. Sixteen patients suffered from petit mal or similar attacks involving brief impairment of consciousness. Some of these patients also suffered from grand mal. Petit mal occurred more frequently in those with severe or extensive cerebral palsy than in those with a mild disability. It was, therefore, a nuisance to the already severely handicapped children rather than a cause, in itself, of serious limitation of activities. Grand mal and attacks of Jacksonian type with more prolonged severe impairment or loss of consciousness were present in 53 patients or approximately 25% of those suffering from cerebral palsy. In the majority attacks occurred between once a month and once a year, in spite of anti-epileptic drugs. The proportion of children suffering from severe cerebral palsy who showed epilepsy was not much higher than the proportion of mildly affected patients. The attacks were, therefore, an important cause of limitation of activities in some patients.

Incidence of Speech Defects

The crude criterion used during the present survey to determine if a child suffered from significant speech defect or not was whether comprehension of what he said was rendered difficult. Minor speech defects which were not sufficiently severe to impair comprehension of what was said were

TABLE 14

NO. OF PATIENTS WITH CEREBRAL PALSY BETWEEN AGES OF 6 AND 11 FOUND REVERSING LETTERS WHEN READING OR WRITING IN A SMALL EDINBURGH SURVEY

Type of Palsy	No. of Patients Questioned	Reading Only	Writing Only	Both Reading and Writing	Totals
Right hemiplegia ..	12	1	4	3	8
Left hemiplegia ..	13	0	1	1	2
Diplegia	24	0	3	2	5
Ataxia and diplegia with ataxia ..	5	0	2	0	2
Dyskinesia	3	0	0	0	0
Totals . ..	57	1	10	6	17

ignored. Generous allowance was made for retardation of speech in children with mental defect.

One hundred and two of the patients (approximately 49%) were considered to suffer from significant speech defects. This may be compared to the figure obtained in one recent series where, in all, 79% of the palsied children of school age were found to suffer from speech defects, including minor defects and probably some patients with aphasia (Dunsdon, 1952). Of the patients in the present series, 10·5% had no more than one or two words of speech and are included in a total of 24·5% who had speech defects of such severity that they could not express their ideas adequately in speech.

Incidence of Visual Defects

Visual defects due to other causes than refractive errors were found in 35 patients (Table 15). The incidence of partial blindness was much higher in patients with severe cerebral palsy and mental defect than in those who were mildly affected. All eight of the patients with bilateral hemiplegia, for example, had only partial vision. In seven patients who were considered to be educable the visual defects were thought to be sufficiently severe to necessitate education by non-visual means, now or in the future. Four of these patients were suffering from retrolental fibroplasia, which was found in six patients in the series in association with diplegia. It was interesting to note the very good compensation achieved by some patients who suffered from severe field defects.

Incidence of Behaviour Disorder

The majority of the children with cerebral palsy in the present series, especially those with acquired cerebral palsy, showed functional behaviour dis-

TABLE 15

ASSOCIATED DISABILITIES AND SCHOOLING IN 208 PATIENTS SUFFERING FROM CEREBRAL PALSY

Classification of Palsy	No. of Cases	Epilepsy		Aphasia	Visual Defect	Speech Defect	Over-activity	Schooling				
		Grand Mal Jacksonian	Petit Mal and Other					Normal School	P.H. School	M.H. School	Inducable	Not yet at School
Hemiplegia												
Mild	27	6	0	2	1	11	3	9	2	8	4	4
Moderately severe ..	26	10	4	6	4	8	4	6	4	5	1	10
Severe	22	8	0	4	6	2	2	8	5	2	4	3
Total	75	22	4	12	11	21	9	23	11	15	9	17
Diplegia												
Paraplegia	29	6	1	0	2	7	0	7	9	5	0	8
Triplegia	23	9	3	3	3	14	0	3	3	5	4	8
Tetraplegia	27	7	5	1	8	14	0	1	0	6	9	11
Total	79	22	9	4	13	35	0	11	12	16	13	27
Diplegia with ataxia												
Triplegia	9	1	2	0	0	8	1	2	3	1	2	1
Tetraplegia	3	0	2	0	1	2	0	0	1	1	0	1
Total	12	1	4	0	1	10	1	2	4	2	2	2
Ataxia	15	3	1	0	2	11	4	2	7	3	0	3
Dyskinesia	17	0	4	0	0	15	1	2	7	2	1	5
Bilateral hemiplegia ..	8	5	0	0	8	8	1	0	0	0	8	0
Other forms of cerebral palsy	2	0	0	0	0	2	0	0	2	0	0	0
Grand total	208	53	22	16	35	102	16	40	43	38	33	54
Percentage		28·4	10·5	7·7	16·8	48·8	7·7	19·3	20·7	18·2	15·9	25·9
Percentage of school age ..								26·0	27·9	24·7	21·4	

order at some time or another, the result of difficulty in adapting to their disability. In addition, a number of children showed a rather typical form of over-activity which was characterized by an intense preoccupation with the immediate surroundings, gross impairment of concentration and attention-span, and complete lack of common sense or insight. These patients were never still. All objects in the room, furniture and people attracted great superficial momentary interest. Objects were handled and frequently put to the mouth, chewed and then discarded. The over-activity appeared to be most severe up the age of 8 or 10 and then gradually to decrease. This form of behaviour disturbance was found in 16 patients and was most frequent in those with hemiplegia, especially when it affected the right side, and was associated with epilepsy (Table 15). Until the over-activity lessened most children suffering from it were ineducable.

Incidence of Aphasia and Dysphasia

Aphasia or dysphasia was evident in 16 patients (approximately 8%) with cerebral palsy. Twelve of the patients suffered from hemiplegia, only one of them on the left. All but two of the 16 aphasic or dysphasic patients suffered from moderately severe or severe cerebral palsy, and a mild or moderate degree of mental defect was present in nine. In all, however, the degree of verbal difficulty was out of all proportion to the severity of the mental impairment. Cases of severe mental defect in which there seemed to be some specific difficulty in comprehension were classified as mental defective but not also as aphasic.

The most important effects of aphasic and dysphasic disorders were seen in the first years at school where a number of the patients were considered to be defective until careful intelligence testing was performed.

Specific Learning Difficulties in Children with Cerebral Palsy

In addition to the handicaps imposed on the child's ability to learn by motor impairment, visual defects, aphasia and speech defects a number of patients showed specific educational difficulties. Some appeared to have great difficulty in recognizing and forming letters, numbers and shapes of small words, and learning to read and write was therefore much retarded. Mild manifestations usually last only a few months and take the form of reversals of letters and small words in writing, and, less commonly, in reading. In its more severe forms, however, the learning disability deserves the name of true word-blindness. Ataxic patients appeared to show particular difficulty in writing letters, and letter reversals and word inversions were especially frequent and severe.

It was impossible to obtain details of the early educational progress of all the children in the survey, but in 57 patients, whose intelligence quotients varied from 60 to 125, details were obtained and the results are shown in Table 14. It will be seen that a relatively high proportion of patients, especially those with right hemiplegia, showed directional confusions in writing.

A high proportion of patients with cerebral palsy showed rather poor powers of concentration and a very limited attention span, even when intellectual impairment was relatively slight. Very skilful teaching is necessary.

The Education of Children with Cerebral Palsy

In Table 15 are shown the numbers of children of school age in the series who attended various types of school or were classified as ineducable. The figures obtained during this survey were compared with those of other similar surveys. The proportions of children in different schools vary in different surveys. This is probably a reflexion on the selective nature of some series and of the differences in the types of schools available in different districts rather than a measure of differences in the types of handicap suffered by children in different areas. Nevertheless, the surveys show that not more than one quarter of the children who suffer from cerebral palsy are capable of benefiting from normal educational methods. Only three patients in the present series were thought to be capable of taking their higher leaving certificates. Over half the patients in normal schools suffered from hemiplegia and, therefore, had at least one functionally normal upper limb. In contrast, only 11 patients with diplegia were in normal schools and there was tetraplegic paresis in only one of these. In general, types of cerebral palsy which tended to involve all limbs resulted in a smaller proportion of children in normal schools. Thus, in spite of the relatively less severe mental impairment than in other forms of cerebral palsy, only two patients with dyskinesia were in normal schools. Of the 12 patients of school age who showed ataxia, there were only two in normal schools.

Thirty-three of the patients of school age (approximately 21·5%) were classified as ineducable. In practice this category was found to consist almost entirely of severely mentally defective children. Thirteen of the patients classified as ineducable were in institutions for the mentally defective. The

remainder were in occupation centres or at home. Twenty-one were bedridden and in need of constant care and attention. Eighty-one of the patients of school age (52·6%) attended special schools for the mentally or physically handicapped. The decision as to which type of school was best for the child was decided on the basis of the relative severity of the palsy and of the intellectual impairment. Though there was some overlapping of the types of case found in these schools; in general, those with intelligence quotients of under 70 were found in schools for the mentally handicapped and those with intelligence quotients of over 70 were in schools for the physically handicapped. Forty-three children, approximately 28% of those of school age, were in schools for the physically handicapped, of whom six were in residential schools.

Prospects of Regular Employment for Children with Cerebral Palsy

During the survey some experience was gained of the employment difficulties encountered by a number of patients between the ages of 16 and 18 who suffered from cerebral palsy. On the basis of this experience an attempt was made to assess the prospects of regular employment and the need for care of the cases of school age ascertained during the survey. Patients were placed in three categories, probably employable, possibly employable, or unemployable (Table 16).

The majority of patients who attended normal schools were considered to be probably employable with the exceptions of two relatively severely affected patients with diplegia, who were placed in the 'possibly employable' group. Three patients with hemiplegia and two with diplegia in schools for the physically handicapped were felt to be probably employable. In all 43 patients, or 28% of those of school age, were considered to be probably employable.

Patients with intelligence quotients of less than 70 were automatically classified as unemployable. Because of intellectual impairment they were only fitted for unskilled manual work, which they were unable to do on account of their physical handicaps. Patients with intelligence quotients of between 70 and 85 might be expected to be suitable for unskilled work, but the majority would only be capable of this if the palsy was of a relatively slight degree. Therefore those who were moderately severely or severely affected were classified as unemployable, and patients with mild cerebral palsy were classified, somewhat optimistically, as being possibly employable. In all 86 patients, approximately 56% of those of school age, were classified as unemployable.

Twenty-five patients were classified as possibly employable, 16% of those of school age. Two cases in this category came from normal schools, 20 from schools for the physically handicapped, including five patients with ataxia and six with dyskinesia. Three patients came from schools for the mentally handicapped. They had intelligence quotients of between 70 and 85 and relatively mild cerebral palsy.

TABLE 16
ASSESSMENT OF PROSPECTS OF EMPLOYMENT IN PRESENT CIRCUMSTANCES OF 154 CHILDREN OF SCHOOL AGE WITH CEREBRAL PALSY

Unemployable Criteria	Nos. of Patients	Possibly Employable Criteria	Nos. of Patients	Probably Employable Criteria	Nos. of Patients
Intelligence quotient below 70					
Hemiplegia	22	Hemiplegia with epilepsy P.H. schools	5	Hemiplegia Normal schools	23
Diplegia	25	Mild hemiplegia M.H. schools	2	Hemiplegia P.H. schools	3
Other	15	Paraplegia P.H. schools	1	Paraplegia Normal schools	7
Total I.Q. under 70	62				
Intelligence quotient between 70 and 85, but severely affected					
Hemiplegia	3	Triplegia Normal schools P.H. ,, M.H. ,,	1 2 1	P.H. schools	1
Diplegia	10	Tetraplegia Normal schools	1	Triplegia Normal schools P.H. ,,	2 1
Other	11	Others P.H. schools	12	Others Normal schools	6
Total I.Q. between 70 and 85	24				
Total unemployable	86	Total possibly employable	25	Total probably employable	43
Percentage	56	Percentage possibly employable	16	Percentage probably employable	28

It seems clear from this somewhat speculative assessment of the chances of regular employment for children with cerebral palsy that not more than one-third are likely to be self supporting in present conditions. A number of the patients who do obtain regular work will obtain only jobs in which prospects are poor. In present labour conditions relatively few of the 16% of children in the 'possibly employable' group are likely to obtain regular employment, though in favourable conditions and under some form of supervision many might make a contribution to their own maintenance.

The 56% of patients in the unemployable group are unlikely to be able to make any contribution to their own maintenance. The majority will be in need of constant care for many years. Twenty-one of the patients in this group are bedridden and probably all will eventually be in need of constant nursing attention in institutions.

Summary and Conclusions

A description has been given of a recent survey in Edinburgh designed to ascertain the incidence of cerebral palsy in children born between 1938 and 1952. Evidence is presented which suggests that the incidence is between 2 and 2·5 cases per 1,000 children, and this estimate is compared with the incidence of the condition found in other surveys.

The number of children suffering from cerebral palsy born between 1950 and 1952 who were ascertained was small. It is shown that this is largely due to the present great delay in the diagnosis of children with early symptoms of cerebral palsy.

A smaller incidence of cerebral palsy was found in the six-year period 1938 to 1943 than in the period 1944 to 1949. It is suggested that the difference in incidence is partly due to more patients with cerebral palsy born in the later period surviving because complicating infections could be controlled by antibiotics. A more important cause of the greater incidence amongst children born between 1944 and 1949 is the fact that the survival rate for those suffering from conditions likely to lead to cerebral palsy was increased in this period by improvements in infant care and the widespread use of antibiotics.

The severity of the handicaps imposed on the child because of cerebral palsy and associated physical and mental abnormalities are described. The relatively low proportion of patients capable of benefiting from normal educational methods, and the high proportion who are likely to be a burden to the community throughout life is stressed. An assessment is presented of the numbers of patients likely to obtain regular employment eventually and the numbers who will require care and attendance.

It is pointed out that earlier diagnosis and treatment of children with cerebral palsy might lead to a reduction of the physical handicap resulting from contractures of the limbs. Though not likely to be financially rewarding, it is apparent as a result of the survey that much more attention must be paid to obtaining training and employment, if necessary under supervision, for patients with cerebral palsy.

This survey could not have been made without the cooperation of so many physicians and surgeons in Edinburgh that it is impossible to mention them individually. I am especially grateful to Dr. W. N. Boog Watson, of the School Medical Service, and Dr. H. P. Tait, of the Maternity and Child Welfare Service, for their unfailing help, and to the paediatricians of the Royal Hospital for Sick Children and Western General Hospital, Edinburgh. I owe thanks to the records officers of these and other hospitals and institutions, and to Miss E. Cruickshank for much secretarial assistance.

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CONGENITAL PNEUMONIA AND PNEUMONIA IN THE NEONATAL PERIOD

AN ANALYSIS OF 84 CASES EXAMINED AT NECROPSY

BY

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Pneumonia is relatively often found at necropsy in stillborn infants and infants dying in the neonatal period. Ahvenainen (1951) found microscopical evidence of pneumonia in 14 of 45 stillborn infants; Arey and Dent (1953) demonstrated pneumonia at necropsy in 31% of 123 infants who died in the neonatal period, and Barter (1953) in 19% of 131 infants who died within six hours of birth. The problems of pneumonia in this age group have recently been discussed in *The Lancet* (Annotation, 1954) and have been treated editorially in *The Journal of Pediatrics* (Blattner, 1953).

In order to assess more closely the importance of pneumonia at this age, the authors have re-examined the necropsy material from the Institute of Pathological Anatomy, University of Oslo. It is the purpose of this paper to give the statistical data of this investigation, and to discuss the findings.

The Material

This consists of 422 consecutive necropsies, namely, all newborn infants sent for necropsy during the six-year period 1948-1953 inclusive. Of these infants, 169 were stillborn and 253 died within the first 30 days of life. We have personally re-examined all microscopical slides of these cases. At necropsy slides were prepared from the heart, liver, kidneys, pancreas, thymus and thyroid gland, and usually four slides from the lungs of each infant. The stain used was haematoxylin and eosin, in some cases supplemented by other stains. The criterion for the diagnosis of pneumonia has been the finding of a marked accumulation of polymorphs in the lung alveoli and the parenchyma.

Results

The distribution of the cases of pneumonia among all infants examined is shown in Table 1. The high incidence (29%) of pneumonia in the heaviest group of stillborn infants is striking.

TABLE 1
INCIDENCE OF PNEUMONIA IN DIFFERENT WEIGHT GROUPS

	Weight at Birth (g.)	No. of Infants Examined	No. of Cases with Pneumonia
Stillborn infants (total 169)	<2,500	57	1 (2%)
	2,500-4,000	88	8 (9%)
	>4,000	24	7 (29%)
Born alive (total 253)	<2,500	102	29 (28%)
	2,500-4,000	129	34 (26%)
	>4,000	22	5 (23%)
Total ..		422	84 (20%)

Fig. 1 shows the distribution of the 84 cases of pneumonia according to weight at birth and age at death. The distribution in relation to birth weight shows the same peculiar feature as in Table 1, i.e., pneumonia in the stillborn is seen particularly in large infants. Their average birth weight was 3·9 kg.

Table 2 illustrates this factor in more detail. It will be seen here that stillborn infants with pneumonia weighed, on an average, 0·9 kg. more than stillborn infants in whom no pneumonia was demonstrable. In infants who lived for more than one week, the relation appears to be reversed, i.e., infants in whom pneumonia was observed weighed,

TABLE 2
AVERAGE BIRTH WEIGHT IN CASES OF PNEUMONIA

	Stillborn	Died within 1 to 7 Days	Died within 8 to 30 Days
Cases with pneumonia (84)*	3·9 kg. (16)	3·0 kg. (56)	2·7 kg. (12)
Cases without pneumonia (338)	3·0 kg. (153)	2·87 kg. (158)	3·1 kg. (27)

* No. of cases in brackets.

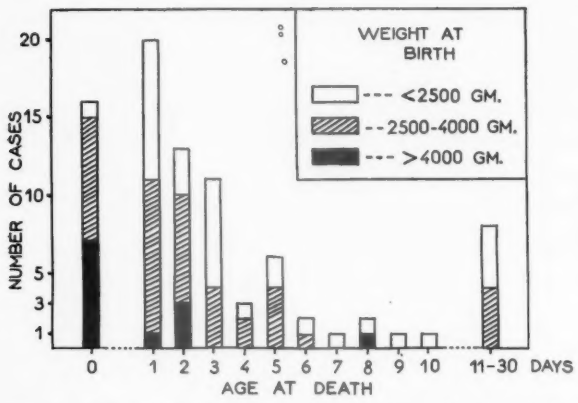

FIG. 1.—The distribution of 84 cases of pneumonia according to weight at birth and age at death.

on an average, 0·4 kg. less than those without demonstrable pneumonia.

Table 3 shows the data regarding pregnancy and labour of the mothers of 16 stillborn infants with pneumonia. It is evident that the sequence was most frequently that of an elderly primipara with an especially large infant, prolonged labour and symptoms of intra-uterine infection. Of the 16 mothers, 15 were primiparae, 12 of them 28 years old or more.

An analysis of the 33 infants who died during the first two days of life, and in whom pneumonia was found, discloses that in 13 cases rupture of the membranes occurred at least six hours before delivery; nine of these were elderly primiparae with febrile labour and large infants. In 12 of the remaining cases there was a history of late rupture, i.e., within the last 20 minutes before delivery. In these cases there was no increase in incidence of elderly primiparae, the delivery being normal in the majority of cases. The post-mortem diagnosis of pneumonia in these 12 infants came as a surprise. There were several examples of massive pneumonia in infants who died 15 to 20 hours after birth. This was most frequently found in premature infants.

We have also endeavoured in our material to clarify the mode of pulmonary infection in newborn infants. On detailed analysis of infants with pneumonia who died during the first three days, these may be divided into two distinct groups according to the mode of infection, as illustrated in Fig. 2. The infants who were probably infected as a result of aspiration of contaminated amniotic fluid had an average birth weight of 3·60 kg. The infants probably infected after delivery had an average birth weight of 2·46 kg., half the number being premature.

Discussion

It should be noted that the figures and tables are prepared from post-mortem material and do not, therefore, give any definite information on the incidence of pneumonia among surviving infants in the same period. Neither has the question been solved whether pneumonia was the actual cause of

TABLE 3

DATA ON 16 STILLBORN INFANTS WITH PNEUMONIA

Necropsy No.	Age of Mother	Parity	Temperature (° C.) of Mother before Delivery (in axilla)	Rupture of Membranes before Birth	Therapy before Birth	Birth Weight (g.)
10/48	35	1	38·4	6 days Foul odour	Penicillin	4,000
21/49	37	1		Same day Cloudy		4,810
39/49	20	1		2 days		3,790
43/49	33	1	Febrile 3 days	At delivery Cloudy		4,280
114/49	26	1		5 days		4,930
11/50	24	1	38·5	Over 1 day Cloudy	Streptomycin	4,620
50/51	41	1	37·8	1½ day Foul odour	Penicillin	2,600
52/51	32	1	Subfebrile	3½ days	Penicillin + streptomycin	3,870
18/52	36	1	38·9	4 days	Penicillin + streptomycin	3,900
49/52	30	1		1 day		1,700
55/52	33	1	37·9	2½ day Foul odour	Penicillin + streptomycin	3,900
66/52	37	1		1½ days		5,040
8/53	26	1		Over 1 day		2,940
20/53	40	2		5 hours		4,200
49/53	28	1		1 day Foul odour		3,630
37/53	29	1		7 days	Penicillin + streptomycin	3,900
Average ..	31·7					3,880

death or only a contributory factor. The fact that pneumonia is seen so frequently 'in the valley of the shadow of birth' (Smith, 1951), emphasizes the importance of an investigation in this field in order to reach effective prophylaxis and therapy.

Clifford (1954) has shown that elderly primiparae relatively often give birth to post-mature infants. Elderly primiparae also frequently have a complicated delivery. Post-maturity in itself, as well as the complications at birth, seems to involve an increased risk of massive intra-uterine aspiration. In these cases early rupture of the membranes often occurs (spontaneous or provoked). The aspirated amniotic fluid is frequently contaminated, providing a possible risk of intra-uterine pneumonia. Thus, the correlation shown here between elderly primiparae, large infants and pneumonia of intra-uterine origin, does not seem to depend on any chance coincidence. It follows that prophylactic antibiotic treatment is specially indicated in elderly primiparae.

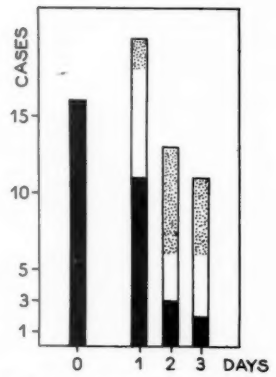

FIG. 2.—Stillborn infants and infants who died during first three days and in whom pneumonia was found (60 cases).
Black: infants probably infected before or during delivery.
Dotted: probably airborne infection.
White: obscure mode of infection.

The clinical diagnosis of pneumonia in the newborn is difficult, as confirmed in this material. The physical findings have been inconclusive, and in many cases x-ray and blood examinations fail to contribute to the diagnosis. Another feature complicating the diagnosis is the normal presence in this age group of a leucocytosis with a shift to the left. Antibiotic treatment of the infants should, therefore, be instituted even on suspicion alone, and should be directed against the micro-organisms empirically known to be active in intra-uterine and airborne infection respectively. In an attempt to clarify which micro-organisms are most frequently causative in these pulmonary infections, we have recently been performing puncture of the lungs through the thoracic wall as soon as possible after death. Results of these studies are not yet available.

Summary

In post-mortem material comprising 169 stillborn infants and 253 infants who died in the neonatal period, pneumonia was observed in 84 infants, 60 of whom were stillborn or died within the three first days.

These 60 cases have been distributed into two main groups: (1) infants infected before or during delivery. Most of these were large infants, and the mothers were, as a rule, elderly primiparae. (2) Infants probably infected after delivery by airborne infection: half of these were premature. Massive pneumonia was seen in premature infants dying during the first day, even after entirely normal births.

The prophylactic treatment of mother and child should be planned to combat both these two modes of infection.

We wish to thank Professor Leif Salomonsen and Professor Olav Torgersen for helpful advice and criticism during the preparation of this paper, and for permission to use the material of their departments.

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HAEMOGLOBIN AND RED CELLS IN THE HUMAN FOETUS

II.—THE RED CELLS

BY

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In a previous paper (Walker and Turnbull, 1953) we have demonstrated the haemoglobin levels and red cell count in the cord blood of the human foetus throughout pregnancy.

From the 10th week to the 24th week the red cell count doubles (from 1,500,000 to 3,000,000), but the haemoglobin rises only from 9 to 15 g. After the 24th week, the red cell count continues to rise till at 40 weeks, in the well oxygenated foetus, it is just under 4,000,000 per c.mm., but the haemoglobin level is unchanged at 15 g. These findings suggest that throughout pregnancy the red cells must be becoming progressively smaller.

If at 40 weeks extra red cells have been produced under the stimulus of anoxia, the haemoglobin level may be 20 g. and the red cell count 5,000,000, the haemoglobin rising by 30%, but the red cell count by only 25% over the levels found at 40 weeks in the well oxygenated foetus (15 g. and 4,000,000). These unequal rises in haemoglobin and red cells under conditions of anoxia suggested therefore that the extra cells produced are somewhat larger or contain more haemoglobin than those normally present in the blood at that time.

Very little information is, however, available from other authors with regard to the characteristics of the red cells in the human foetus during pregnancy. Wintrobe and Shumacker (1935, 1936) studied 12 foetuses, obtained at hysterectomy, and three premature infants, all live born, at intervals from the 76th to the 252nd day of pregnancy. Their findings suggest that the packed cell volume increases gradually as pregnancy advances and that the red cell size and the number of immature red cells steadily diminish.

Many investigators have, however, studied the red cells in the cord blood of the infant at birth (presumably at or near full-term) and some of the results are shown in Table 1. It is seen that, while the mean readings of packed cell volume vary from 50·8 to 56% the range covered (40-60%) is very similar in each series. There is reasonable agreement amongst the authors that the mean cell volume and mean cell haemoglobin are, at birth, above

TABLE 1

PACKED CELL VOLUME, MEAN CELL HAEMOGLOBIN, MEAN CELL VOLUME, MEAN CELL HAEMOGLOBIN CONCENTRATION AND RETICULOCYTE LEVELS IN HUMAN CORD BLOOD AT BIRTH

Reference	No. of Cases	Packed Cell Volume (%)		Mean Cell Haemoglobin (γγ.)		Mean Cell Volume (c.μ)		Mean Cell Haemoglobin Concentration (%)		Reticulocytes (%)	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Mugrage and Andresen (1936)	40	53·18	(42-62)*	35·1	(30-40)*	108·9	(99-120)*	32·2	(30-35)*		
Guest *et al.* (1938)	34			37·5		113	(90-124)				
Waugh *et al.* (1939)	41									2·7	(0·2-5·0)
	51	51·3	(41-61)								
De Marsh *et al.* (1941)	16	51·0	(38-59)								
Findlay (1946)	17										0 -6·0
	11	50·8	(40-61)								
Gairdner *et al.* (1952)	12	56		33·7		107		31·8		3·5	

* Calculated from author's data.

normal adult levels and that there is a high reticulocyte count, suggesting that the cells are larger than adult cells, and that there are still a number of immature cells in the blood.

In this paper the behaviour of the red cells is studied throughout pregnancy, with reference to the packed cell volume, the reticulocyte count, the mean cell diameters (which have been measured) and the calculated absolute values of red cell characteristics (mean cell haemoglobin, mean cell volume, mean cell haemoglobin concentration). We have also studied the features of the extra cells produced in response to anoxia. As in our previous paper the samples were taken at birth from the cord vessels of live-born foetuses and infants in the Aberdeen Maternity Hospital. The methods of selection of cases and of classification into clinical groups is similar to that detailed previously.

Techniques

Packed Cell Volume. At delivery at least 1 ml. of blood was withdrawn from the umbilical vein into a clean dry syringe and placed in a test-tube in which 2 drops of Wintrobe solution had been evaporated to dryness. Wintrobe haematocrit tubes were used and 0·7 ml. of blood was centrifuged at 3,000 r.p.m. for 30 min. The packed cell volume (excluding white cell layer) was read without correction for trapped plasma.

Mean Cell Diameter. A photographic technique (Adams, 1954) was employed. The image of a thinly spread blood film stained with Leishman's stain was projected from a horizontally placed microscope downwards on to Kodak bromide foil card photographic paper. The height of the microscope was adjusted so that the image of the cells was magnified exactly 1,000 times. This type of paper has a high dimensional stability and can be developed without shrinkage or distortion. Two or three suitable fields were selected from each film and photographed. The diameter of the red cells was measured using an accurately calibrated 8-cm. square glass grid with a centimetre/millimetre scale. If a cell was ovoid, the average of the greatest and smallest diameters was taken. Crenated or badly distorted cells were not measured nor were those at the periphery of the film to avoid errors due to spherical aberration. In each case 500 cells were measured to the nearest 0·5 μ.

Reticulocytes. The reticulocyte preparations were vitally stained using brilliant cresyl blue and counterstained with dilute Leishman's stain. The number of reticulocytes was then enumerated in 1,000 red blood cells.

Absolute Values. The mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration were calculated by means of the usual formulae (Whitby and Britton, 1950).

Findings

Packed Cell Volume. Readings of the packed cell volume in 143 cases of clinically normal pregnancy are shown in Fig. 1. There is a wide scatter in the readings, especially in early pregnancy, resembling the scatter in the red cell counts at this time. Regression lines have, however, been calculated for the periods 1 to 22 and 36 to 43 weeks to show mean values.

The packed cell volume rises from a mean value of 31·6% at the tenth week to reach 40·5% at the 22nd week (probably 42 to 45% by the 23rd to 25th weeks). There are very few readings from then until the 36th week, but the results suggest that there is little, if any, rise in the packed cell volume over this period. From the 36th week onwards the results spread out. While many remain within the

FIG. 1.—Packed cell volume levels in cord blood of the human foetus in normal pregnancy.

range of 42 to 45% the majority are much higher and the mean value rises steadily. If pregnancy continues after the 41st week the mean values continue to rise and readings within the normal adult range (42 to 47%) are no longer found (Table 2). At the 43rd week one reading of 66% (haemoglobin 19·5 g. and red cell count 5,320,000) was found.

TABLE 2
PACKED CELL VOLUME LEVELS IN CORD BLOOD OF THE FOETUS IN NORMAL LATE PREGNANCY

Menstrual Age	Packed Cell Volume (%)	
	Mean	Range
38	47·8	43 – 51
39	49·4	41·5– 56
40	51·3	46 – 60
41	53·4	43 – 59
42	54·9	49 – 63
43	58·6	52·5– 66

When the pregnancy was complicated by pre-eclampsia, where abortion had threatened earlier, or foetal distress was manifest the readings were, in most cases, higher than readings in normal cases at the same stage of gestation. This is only to be expected, since such cases have, as we have shown previously, higher red cell counts than normal cases. In Fig. 2, for example, the readings in 42 cases of pre-eclampsia are seen. In cases of placenta praevia the readings for the packed cell volume were within normal limits.

Mean Cell Volume. Estimations in 143 cases of clinically normal pregnancy are seen in Fig. 3. Regression lines have been calculated to demonstrate the mean values. At the 10th week a mean value of 191 c.μ was found, but by the 22nd week the mean value was 141·3 c.μ. After this time insufficient cases are recorded, but it would appear that there is a slow fall in the mean cell volume until about the 36th week when the mean value was 116·8 c.μ. At each week after the 36th the mean varied only from 115 to 118 c.μ and this level was maintained till the 43rd week. The regression line from the 36th to 43rd week is level at 116·8 c.μ and there does not appear to be any fall in the mean cell volume over this period.

When mean cell volume estimations were performed in cases complicated by pre-eclampsia, threatened abortion earlier in the pregnancy, or foetal dis-

FIG. 3.—Mean cell volume readings in cord blood of the human foetus in normal pregnancy.

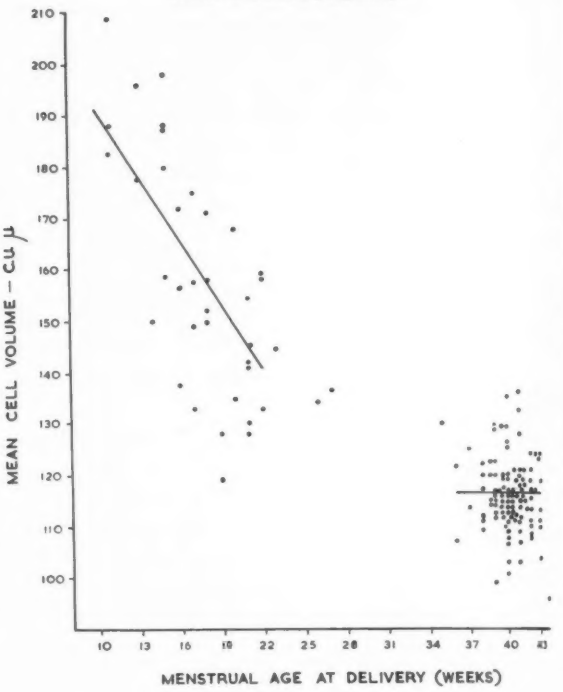


FIG. 2.—Packed cell volume levels in cord blood in pre-eclampsia.

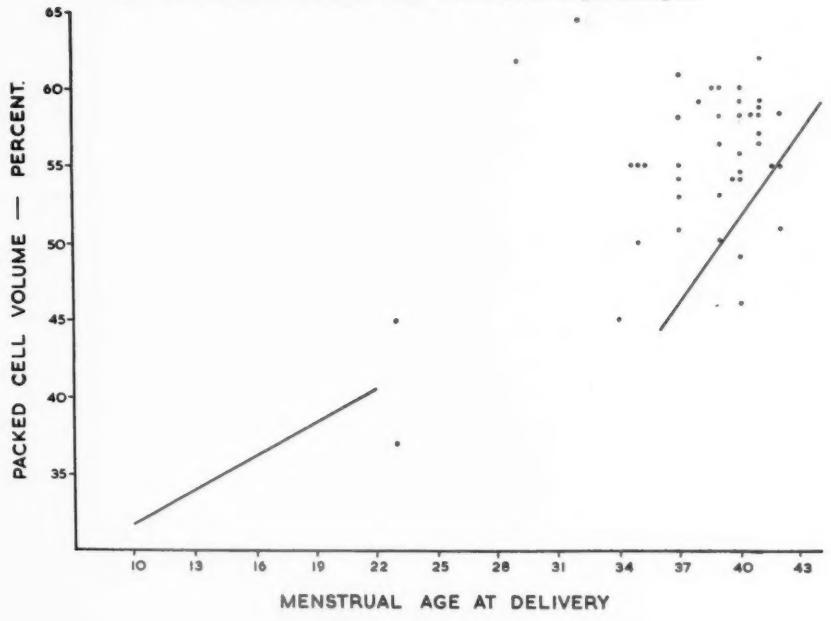
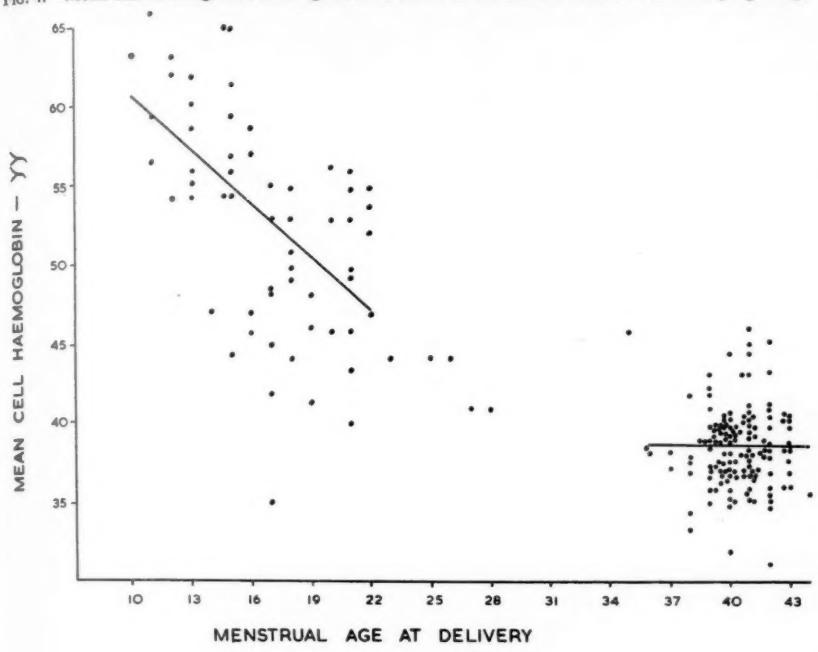


FIG. 4.—Mean cell haemoglobin readings in cord blood of the human foetus in normal pregnancy.



tress, no difference could be demonstrated from the findings in normal cases. The readings were grouped round the regression lines as were the normal readings and the mean values at each week for normal and abnormal cases were very similar.

Mean Cell Haemoglobin. The findings in a series of 200 cases of normal pregnancy are shown in Fig. 4. There is quite a marked scatter among the readings, but nevertheless, a fairly clear pattern can be seen. The calculated regression lines show that the mean cell haemoglobin falls rapidly from a level of 60·5 $\gamma\gamma$ at the 10th week to reach 47·0 $\gamma\gamma$ at the 22nd week. In this period from 22 to 36 weeks there are only six readings recorded, but from these it appears that the mean cell haemoglobin continues to fall rapidly at first and gradually later. During the last few weeks of pregnancy there is considerable variation among the findings, but the mean value at each week till the 43rd week varies only between 37 and 39 $\gamma\gamma$ (regression line at 38·6 $\gamma\gamma$). The distribution of the findings in cases of pre-eclampsia, previous threatened abortion and foetal distress was again similar to that seen in the normal cases. The mean readings in the abnormal cases after the 36th week varied also from 37 to 39 $\gamma\gamma$.

No statistical difference was found to exist between the readings from normal and abnormal cases with regard to mean cell volume and mean cell haemoglobin levels.

Mean Cell Haemoglobin Concentration. The findings in 143 normal cases are seen in Fig. 5. Unlike the estimations already studied, it appears that the mean cell haemoglobin concentration changes little throughout pregnancy, although there is some variation in individual cases at each stage. From the 10th to the 25th week and 36th to 43rd week 90%

FIG. 5.—Mean cell haemoglobin concentration levels in cord blood of the human foetus in normal pregnancy.

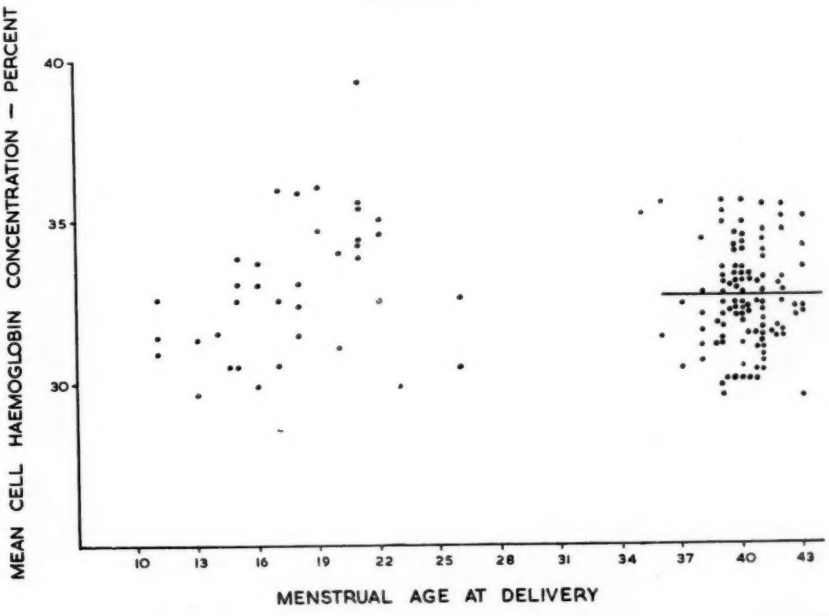


FIG. 6.—Reticulocyte levels in the cord blood of the human foetus in normal and abnormal pregnancy.

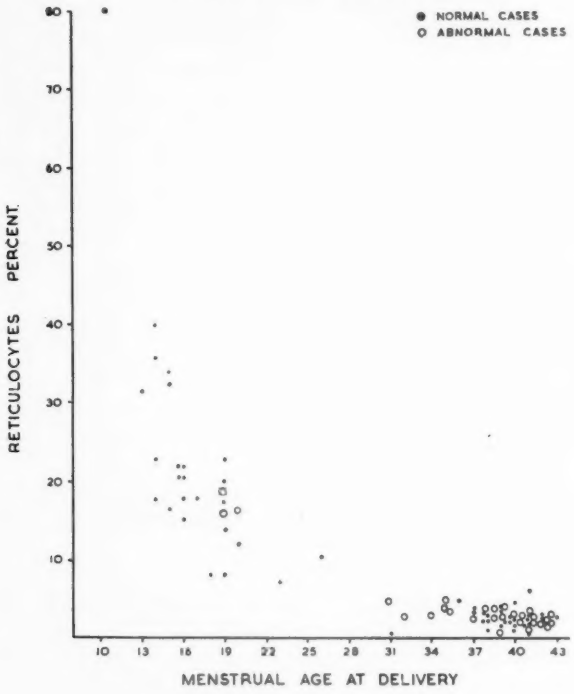
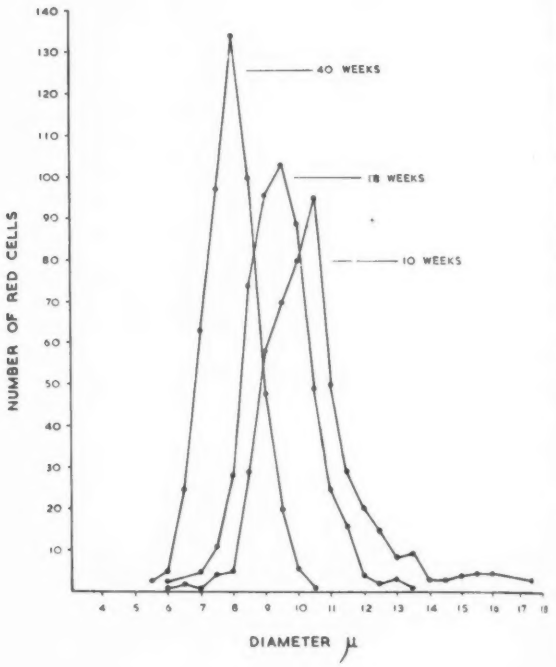


FIG. 7.—Red cell distribution curves in three foetuses of 10, 18 and 40 weeks gestation.



of the readings lie between 30 and 35%. In cases of abnormal pregnancy the values obtained were also between 30 and 35%.

Reticulocytes. In Fig. 6 the findings in 82 cases (54 normal and 28 abnormal) are shown. At 10 weeks only one estimation was performed but 80% of the cells were reticulocytes. At the 14th week readings vary between 20 and 40%, but by the 25th week the average appears to be 10%. There is then a slower fall, until by the 36th week only 2 to 3% of the cells were reticulocytes and this value was maintained until the 43rd week (the range after the 36th week is 0·7 to 5·7%). It can be seen that in abnormal cases (complicated by pre-eclampsia, previous threatened abortion or foetal distress) no variation in the reticulocyte readings was found. We could find no correlation in the later weeks between the haemoglobin level, the red cell count and the reticulocyte values.

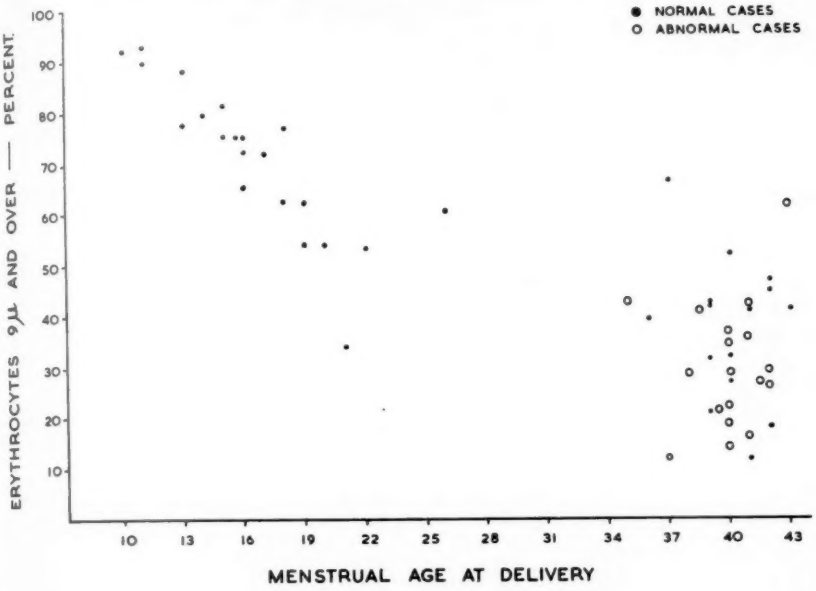
Mean Cell Diameter. The mean cell diameter from the 10th to the 43rd week is seen in Table 3. At the 10th to 11th weeks the mean is high and the range is wide. There is a steady fall till about the 20th week and very large cells (over 12·5 μ) are, by

TABLE 3

RED CELL DIAMETER FINDINGS IN CORD BLOOD OF THE FOETUS THROUGHOUT PREGNANCY

Menstrual Age	No. of Cases	Red Cell Diameter (μ)		Menstrual Age	No. of Cases	Red Cell Diameter (μ)	
		Mean	Range			Mean	Range
10	1	10·5	6 –17·5	22	1	8·8	6 –11·5
11	2	10·2	6 –16	26	1	8·9	6·5–11·5
13	2	9·8	6·5–15·5	35	1	8·6	5·5–12
14	1	9·5	7 –12·5	36	1	8·5	5·5–12
15	2	9·5	6 –13	37	2	8·5	5·5–12
16	4	9·3	6 –13	38	1	8·3	5·5–10·5
17	1	9·2	7 –11·5	39	5	8·5	5·5–11·5
18	2	9·3	6 –13·5	40	10	8·3	5 –11·5
19	2	8·9	6·5–11·5	41	5	8·3	5 –11
20	1	8·8	5·5–11	42	6	8·4	5 –11
21	1	8·4	6 –10·5	43	2	8·8	4 –12

FIG. 8.—Proportion of red cells 9 μ and over in the cord blood of the human foetus in normal and abnormal pregnancy.



that time, no longer seen. There is after that time very little change in the mean cell diameter or in the range of cell size. The changing pattern is illustrated in Fig. 7 where curves have been drawn of the results in three foetuses in the 10th, 18th and 40th weeks of pregnancy. At 10 weeks the base of the curve is wide and the peak is at 10·5 μ. As pregnancy progresses the base narrows, the peak becomes higher, and the whole curve shifts to the left. The mean diameter gradually diminishes as the proportion and number of small cells increase.

Cell Size. At the 10th to 11th weeks the cells vary from 6 to 17·5 μ but 90% are at least 9 μ in diameter (Fig. 8). The wide range of cell size lessens as pregnancy progresses and by the 20th to 22nd week cells over 13 μ are no longer seen, 50% are 9 μ or more, and the majority of the remainder are 8 or 8·5 μ. At this stage only 10% of the cells are 7·5 μ or less (Fig. 9). No cases have been examined from then till the 36th week. From the 36th to 43rd week there is a great variation in the size of cells in the blood of different foetuses. While about 50% of the cells are 8 to 8·5 μ in diameter (Fig. 10) the remainder may be composed of any mixture of large and small cells.

Throughout pregnancy the red cell count increases steadily and we have constructed Fig. 11 from the mean figures for cell size at 10, 22 and 40 weeks to show the number of cells of each size in 1 c.mm. of blood (the mean readings for red cell count are taken from Walker and Turnbull, 1953). It will be seen that there is a steady rise in the total number of cells less than 9 μ in size but that the number of large cells falls only slightly from 1,430,000 to 1,230,000. In the late weeks of pregnancy there may be, however, as we have shown, great variation in the numbers of large and small cells in the blood of individual foetuses and in Fig. 12 is seen the possible

FIG. 9.—Proportion of red cells 7·5 μ and less in the cord blood of the human foetus in normal and abnormal pregnancy.

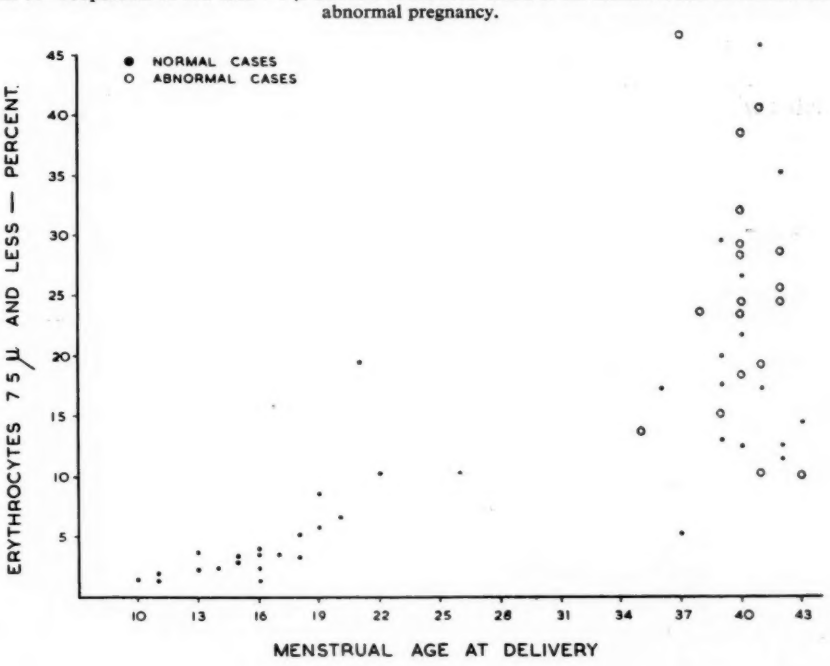
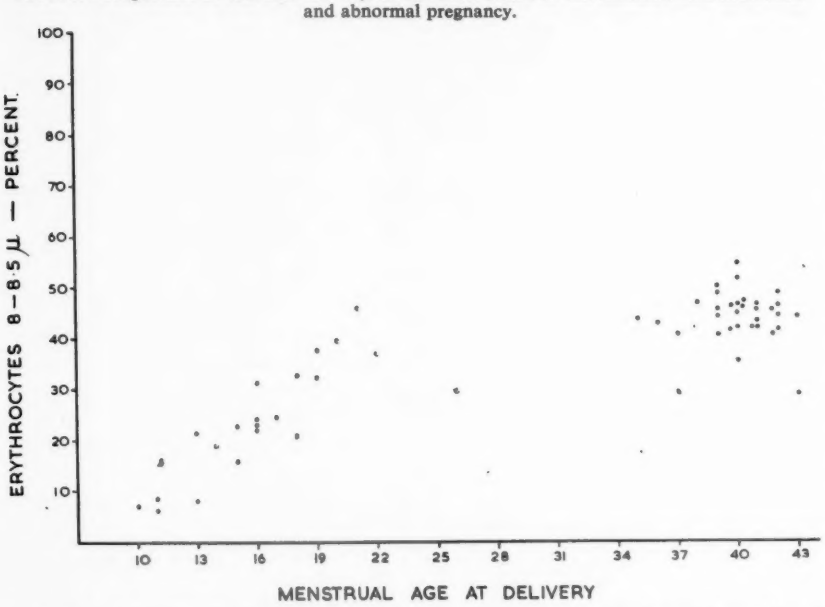


FIG. 10.—Proportion of red cells 8-8·5 μ in the cord blood of the human foetus in normal and abnormal pregnancy.



variation in number of cells of each size. In 10 cases at 39 to 43 weeks, with less than 20% of small cells, there was an average of 0·73 million small and 2·12 million large cells. In five cases, with more than 30% small cells there was, on average, 1·79 million small and 0·76 million large cells. The medium-size cells (8 and 8·5 μ) remained unchanged in both series at 2·09 million.

Discussion

During intra-uterine life red cell production is influenced mainly by the normal process of growth and maturation but a fall in the oxygen supply to the foetus will stimulate the production of extra cells.

Growth and Maturation. At the 10th to 11th week the red cell count is about 1,500,000 and 80% of the cells are reticulocytes. The cells are large, the mean cell volume 190 c.μ and the mean cell diameter 10·5 μ. While over 90% of the cells were 9 μ or over in diameter, there was a wide range of sizes (6 to 17·5). As the cells are few in number, but large, the mean cell haemoglobin is high, 65 γγ.

From the 10th to the 22nd/23rd week the red cell count rises to about 3,000,000 and the haemoglobin to normal adult levels. The red cell count doubles in this period, but the packed cell volume rises by only about one-third (31·6% to 40-42%) since the increase in the count is due to smaller cells, the number of cells over 9 μ remaining unaltered. The influx of smaller cells and the disappearance of cells over 13·5 μ in size causes the fall in the mean cell volume to 140 c.μ and the mean cell diameter to under 9 μ. The increasing maturity is seen in the disappearance of the very large cells and by the fall in the reticulocyte count to 10%. The fall in the mean cell haemoglobin is explained by the decrease in cell size as the mean cell haemoglobin concentration is little altered.

In the late weeks of pregnancy changes due to maturation of the cells are greatly modified by the superimposed effects of anoxia.

The Red Cells in the Later Weeks. We have shown (Walker and Turnbull, 1953) that in the second half of pregnancy the haemoglobin level in

FIG. 11.—Mean distribution of erythrocytes at 10, 22 and 40 weeks.

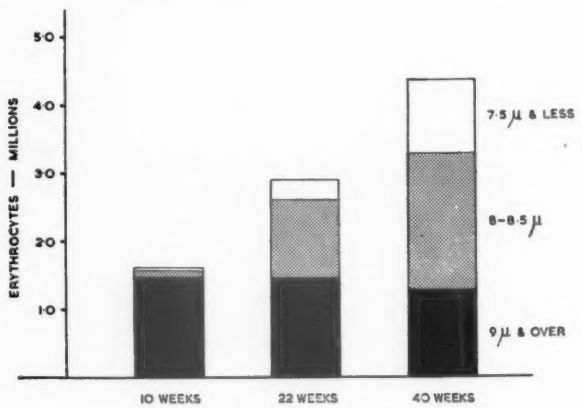
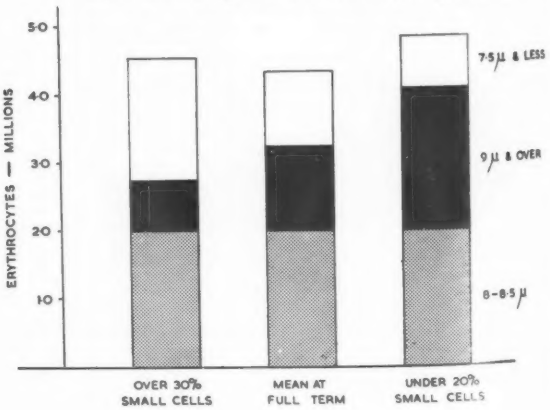


FIG. 12.—Distribution of erythrocytes at full term where over 30 per cent. and under 20 per cent. of cells are 7·5 μ or less.



the cord blood is an index of the efficiency of the oxygen supply. When the oxygen supply is good the haemoglobin level remains at 14·8 to 15 g. but the red cell count as a normal 'growth' process rises steadily to reach about 4,000,000 at 40 weeks. When the oxygen supply is less good the haemoglobin may be 20 g. and the red cell count 5,000,000.

We have shown earlier in this paper that except for the packed cell volume, the findings in the blood of infants in the later weeks from cases of pre-eclampsia, or foetal distress, or where abortion had threatened earlier, cannot be shown to be different from the findings in clinically normal pregnancies. In our first paper we demonstrated that such clinical groupings were useful to distinguish infants likely to have suffered intra-uterine anoxia. Such a clinical grouping is, however, of limited value in the present study since in both abnormal and apparently normal cases a deficiency of oxygen is indicated by a high haemoglobin level and red cell count. The haemoglobin level in the cord blood of the foetus is, therefore, a clearer indication of efficiency of oxygen supply, in the individual case, than the clinical features of the pregnancy.

By using the haemoglobin level as an index of oxygen supply it is possible to distinguish the normal growth and maturation changes in the later weeks from the superimposed changes due to anoxia.

The Packed Cell Volume. Table 4 shows the relation between the haemoglobin level, the red cell count, the packed cell volume and the absolute characteristics of the red cells. It will be seen that there is a close correlation between the haemoglobin level, red cell count and packed cell volume. Where the oxygen supply to the foetus is good and the haemoglobin remains below 16 g. the packed cell volume is 46·5 (±0·7), which is within normal adult levels, although this is achieved by a smaller number of somewhat larger cells than in the adult. When, however, the haemoglobin level is raised in response to anoxia the red cell count and packed cell volume rise. It will be seen from Fig. 1 that in some cases in the 39th to 41st weeks the packed cell volume is no higher than in others at the 22nd to 24th weeks. In such cases the increase in the red cell count (to 4,000,000) has been achieved by the addition of very many small cells and a marked fall in the number of cells over 9 μ in size, the haemoglobin remaining at 14·8 g. In such bloods the mean cell volume at 40 weeks is at or about 100 c.μ (Fig. 3).

The Mean Cell Volume. The findings in Fig. 3 suggest that there is no fall in the mean cell volume as the foetus becomes older after the 36th week, but we would have expected that, as a normal growth change, the mean cell volume would fall steadily and that especially after the 41st week much lower values would be found. Our results were, therefore, submitted to statistical analysis on the theory that anoxia (manifest by a high haemoglobin reading) might be masking the normal maturation pattern. Analysis* has shown that, provided the readings of mean cell volume are adjusted to a standard haemoglobin reading, there is a slight but not significant fall from the 39th to the 41st week, and a significant fall thereafter. What is even more important is that the high mean cell volumes over this period are in most cases associated with high haemoglobin readings and low with low.

* See page 110.

TABLE 4

RELATION BETWEEN HAEMOGLOBIN LEVEL, RED CELL COUNT, PACKED CELL VOLUME, AND ABSOLUTE VALUES OF THE RED CELL CHARACTERISTICS BY WEEKS' GESTATION AND HAEMOGLOBIN LEVEL

No. of Cases (Normals + Abnormals)	Weeks' Gestation	Haemoglobin (g.)		Red Cell Count (c.mm.)	Packed Cell Volume (%)	Mean Cell Haemoglobin (γγ)	Mean Cell Volume (c.μ)	Mean Cell Haemoglobin Concentration (%)
		Range	Mean					
22	39–41	14·8–16·1	15·4	4·15 ±0·06	46·5 ±0·7	37·19 ±0·44	112·4 ±1·6	33·15 ±0·34
56	39–41	16·3–17·6	17·0	4·45 ±0·04	52·2 ±0·4	38·25 ±0·27	117·5 ±1·0	32·60 ±0·21
57	39–41	17·8 and over	18·8	4·89 ±0·04	57·5 ±0·4	38·50 ±0·27	117·9 ±1·0	32·71 ±0·21
11	42	16·3–17·6	16·7	4·34 ±0·08	50·3 ±1·0	38·64 ±0·62	115·4 ±2·2	33·54 ±0·48
18	42	17·8 and over	18·5	4·89 ±0·06	56·4 ±0·8	37·87 ±0·48	115·3 ±1·7	32·90 ±0·37
11	43–44	17·8 and over	19·2	5·15 ±1·0	58·5 ±1·0	37·50 ±0·62	113·5 ±2·2	33·16 ±0·48

It appears, therefore, that, as a normal growth process, the mean cell volume falls steadily as the foetus grows older. In many foetuses in late pregnancy, however, a deficiency of oxygen supply forces the production of red cells, which are on the whole larger than the mean size in the blood at that time, so that in the cord blood at birth in many cases mean cell volumes over 116 c.μ will be found in association with red cell counts of about 5,000,000.

Cell Size. We had hoped, on the evidence of the mean cell volume, to demonstrate clearly that the extreme variation in cell sizes in individual bloods in late pregnancy would be clearly related to the haemoglobin level. Our figures show that, on average, bloods with the highest red cell counts have the greatest number of cells over 9 μ in size, but there is a marked individual variation and the correlation, though present, is not statistically significant. It will be noted, however, from a study of Figs. 11 and 12 that in the blood of some infants there are many more cells over 9 μ in size (in each unit volume) at 40 weeks than are found at 22 weeks. These large cells are rarely seen in the blood of the normal infant after the sixth week (van Creveld, 1932) and must represent a foetal type of haemopoiesis and the large numbers found in some bloods in the late weeks may represent extra cells produced in response to anoxia.

At birth at the 39th to the 43rd week the cord blood will show red counts varying from 4,000,000 to 5,000,000, packed cell volume varying from 41·5 to 66%, and a mean cell volume varying from 100 to 130 c.μ, the higher levels in each case being found in association with high haemoglobin levels and due to the superimposed effect of anoxia on the normal growth pattern. Although large cells over 12·5 μ in diameter are no longer seen, some 10 to 60% of the cells measure more than 9 μ in diameter. The reticulocyte count varies from 0·7 to 5·7%, but we are unable to explain the scatter and found no correlation between the reticulocyte count and the red cell count.

* The mean cell volume (M.C.V.), haemoglobin (Hb), and menstrual age in weeks (W.) were given for 175 infants. Normal pregnancies and others were considered together without distinction.

The regression of M.C.V. on W. and Hb was calculated.

$$\text{M.C.V.} = \underset{\pm 0\cdot53}{-1\cdot13\,\text{W.}} \quad \underset{\pm 0\cdot06}{+0\cdot19\,\text{Hb.}} \quad +139\cdot6$$

The coefficient of W. is significant ($P<0\cdot05$) and that of Hb highly significant ($P<0\cdot01$).

The equation is in agreement with the suggestion that high mean cell volume readings are associated with high haemoglobin readings, but that the mean cell volume tends to decrease with increasing menstrual age.

Table 5 shows the mean values of M.C.V. and haemoglobin for each week of menstrual age from 39 to 44, and the mean M.C.V. adjusted to Hb 120 (a convenient value close to the overall mean of 119·3). The adjusted value is obtained by calculating M.C.V. −0·19 (Hb −120).

The differences between the adjusted values for 39, 40 and 41 weeks are not significant, but there are significant differences between weeks 41 and 42 ($P<0\cdot05$) and 42 and 43 ($P<0\cdot01$).

TABLE 5
RELATION BETWEEN MEAN CELL VOLUME AND MENSTRUAL AGE

Weeks' Gestation	No. of Cases	Mean Haemoglobin (%)	Mean of Mean Cell Volume (c.μ)	Adjusted Mean of Mean Cell Volume (c.μ)
39	30	116·0	116·7	117·4
40	62	116·6	116·8	117·4
41	43	121·8	117·1	116·7
42	29	120·4	115·3	115·2
43+	11	130·5	113·5	111·5

Summary

The red cells in the cord blood of the human foetus have been studied from the 10th to the 43rd weeks of pregnancy. The packed cell volume, the mean cell diameter and the reticulocyte count have been measured and the absolute values of the red cell characteristics calculated.

As pregnancy progresses the red cells as a whole become more mature. The Price-Jones curve shifts to the left, the base narrows and the peak becomes higher.

Three groups of cells have been studied in detail; 9 μ and over, 8 and 8·5 μ, 7·5 μ and under. It is shown that as pregnancy progresses the number of cells less than 9 μ in size in each unit volume of blood gradually increases, while the numbers which are 9 μ and over remain nearly unchanged. There is, however, in the later weeks a wide variation in the number of large and small cells in the blood of different infants.

Deficiency of oxygen supply to the foetus in the later weeks of pregnancy alters the red cell pattern from that seen under normal conditions of growth and maturation. Variation in the oxygen supply *in utero* of the individual foetuses is responsible for the scatter in readings of packed cell volume and mean cell volume in the cord blood at birth and possibly for much of the variations in number and proportion of cells of various sizes.

We are greatly indebted to Dr. F. H. C. Marriott for all statistical analyses reported in this paper.

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HAEMOGLOBIN AND RED CELLS IN THE HUMAN FOETUS

III.—FOETAL AND ADULT HAEMOGLOBIN

BY

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In 1866 Körber found chemical differences between haemoglobin obtained from human placental blood and that from normal adult blood. Since then it has been clearly demonstrated that there are many important differences between human and animal and between foetal and adult haemoglobins (Krüger, 1888; Bischoff and Schulte, 1926; Haurowitz, 1930, 1935; Trought, 1932; Brinkman, Wildschut and Wittermans, 1934; Hill, 1935; Brinkman and Jonxis, 1935; Jope and O'Brien, 1949).

Haselhorst and Stromberger (1930, 1932) showed that the blood of the human foetus possessed a higher affinity for oxygen than that of its mother, but Hill (1935) found that human foetal haemoglobin had a lower affinity than human adult haemoglobin. This apparent anomaly was explained by the work of McCarthy (1943), who showed that the affinity of the haemoglobins for oxygen was greatly modified when they were within a corpuscle. Adult corpuscles caused a marked decrease in the oxygen affinity of their contained haemoglobin, while foetal corpuscles had little effect on the affinity of foetal haemoglobin for oxygen. Recently, Allen, Wyman and Smith (1953) have re-studied the oxygen affinity of human haemoglobins. Unlike Hill (1935) and Haurowitz (1935) they found no difference between the affinity for oxygen of the haemoglobin of the human foetus and that of its mother, provided that the haemoglobin solutions were so treated that the concentrations of dialysable substances were identical. They also found that the haemoglobin from one foetus at 31 weeks had the same affinity as the haemoglobins of term foetuses and of their mothers.

Most investigators have been concerned with a study of the physical, chemical and other characteristics of human haemoglobins, and little information is available of the relative proportions of each type of haemoglobin in the blood of the human foetus at various stages of gestation, although such information is available for the sheep foetus. Karvonen (1949) found that adult haemoglobin first appeared in the sheep foetus at or about the 105th day and that at term 50% of the haemoglobin was adult in type. Beaven, Hoch and Holiday (1951), in one human foetus, at 20 weeks' gestation, found that 6% of the haemoglobin was of the adult type and Schulman (1953) that there was at least 10% adult haemoglobin in the blood of premature infants. Many investigators have, however, studied the proportion of adult haemoglobin in the cord blood of the foetus at birth, at or near full term, and their results are shown in Table 1, from which it can be seen that

TABLE 1
PERCENTAGE OF ADULT-TYPE HAEMOGLOBIN IN HUMAN CORD BLOOD AT BIRTH

Reference	Adult Haemoglobin (%)
Haurowitz (1930)	20
Brinkman *et al.* (1934)	20
Jonxis (1949)	2-25
Ponder and Levine (1949)	20·3
Beaven *et al.* (1951)	20
Zeisel (1951)	16-30
Chernoff and Singer (1952)	15-50
Schulman (1953)	29 (11-55)

the adult fraction contributes, on average, about 20% of the total haemoglobin, but that wide variations exist.

This investigation was planned to study the proportion of adult haemoglobin in the blood of the human foetus throughout gestation and was performed in association with our studies of oxygen levels, haemoglobin levels and red cell characteristics in the blood of the human foetus (Walker and Turnbull, 1953; Turnbull and Walker, 1954). Normal and clinically abnormal cases were studied, and the methods of selection of cases and of clinical classification were as described in previous papers.

Technique

At delivery 1 ml. of blood was removed from the umbilical vein into a syringe, the barrel of which had previously been wetted with a heparin solution. The proportion of adult haemoglobin was estimated (E.P.N.T.) by the technique of alkali denaturation originally described by Brinkman and Jonxis (1936) modified by Jonxis (1952).

Results

Fig. 1 shows the percentage of adult haemoglobin found in the blood of the human foetus throughout gestation in a series of 131 cases. Of these, 98 were normal and of the others, 18 were of pre-eclampsia, 17 of foetal distress, and in three abortion had threatened earlier in the pregnancy. It is seen from a study of the scattergram that no difference exists between the findings in the normal and abnormal cases.

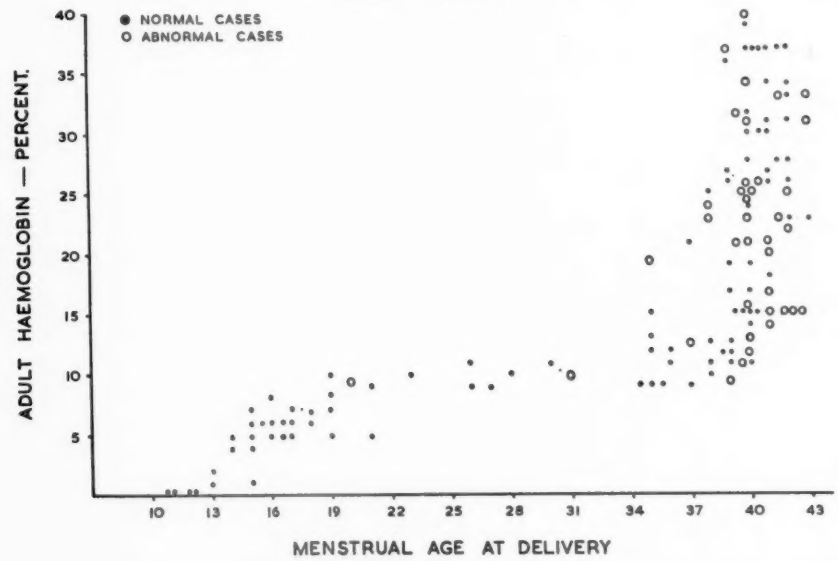
In the four samples examined from foetuses at the 11th and 12th weeks' gestation the haemoglobin was entirely of the alkali-resistant foetal type. The adult type was first noted in the two cases at the 13th week when it constituted 1 and 2% of the total haemoglobin. The proportion increased gradually during the early weeks of pregnancy until at the 22nd to 24th weeks the level had risen to 10%. The six cases studied from then until the 35th week suggest that, during that period, the amount of adult haemoglobin remains fairly steady at or about that level. After the 35th week the readings begin to spread out, and, although in a few cases the level remains at or about 10% until the 41st week, the great majority of readings are much higher. At 40 weeks the proportion of adult haemoglobin ranges from 11 to 39% with a mean value of 22·2%. When pregnancy proceeds beyond the 40th week the proportion of adult haemoglobin in the foetal blood appears to increaseand the mean value at 41 and 42 weeks was 30·7%.

Relation between Adult and Foetal Haemoglobin and Anoxia

The most significant finding in our study, and in those of other investigators quoted in Table 1, is the marked variation in the percentage of adult haemoglobin found in the blood of individual foetuses at term. Most investigators, including ourselves, find a mean reading at or about 20%, but individual bloods may have 5 to 55% of their haemoglobin as the adult type. We have shown previously (Walker and Turnbull, 1953) that the haemoglobin level in the cord blood of the individual foetus at term may vary from 15 to 21 g. per 100 ml. depending on the degree of anoxia to which the foetus had been subjected in the days preceding birth. We considered that the wide scatter in readings in the percentage of adult haemoglobin in the cord blood at birth might be, in some way, related to the degree of anoxia and therefore to the total haemoglobin level (foetal+adult) in each unit volume of blood. This approach was, however, complicated by the probability that increasing foetal age was also responsible for an alteration in the proportions of the two haemoglobins.

The findings in 71 cases delivered between the 39th and 43rd weeks of gestation were first recalculated so that the results in each case were expressed in g. per 100 ml. of blood (for example, if there was 20% adult haemoglobin in a blood with a total haemoglobin of 20 g. per 100 ml. then the results were expressed as total haemoglobin 20 g., foetal 16 g., adult 4 g.). The findings were then submitted to statistical analysis to study the effects of foetal age and total haemoglobin independently on the amount of each type of haemoglobin in a unit volume of blood.

FIG. 1.—Percentage of adult-type haemoglobin in cord blood of the human foetus in normal and abnormal pregnancy.



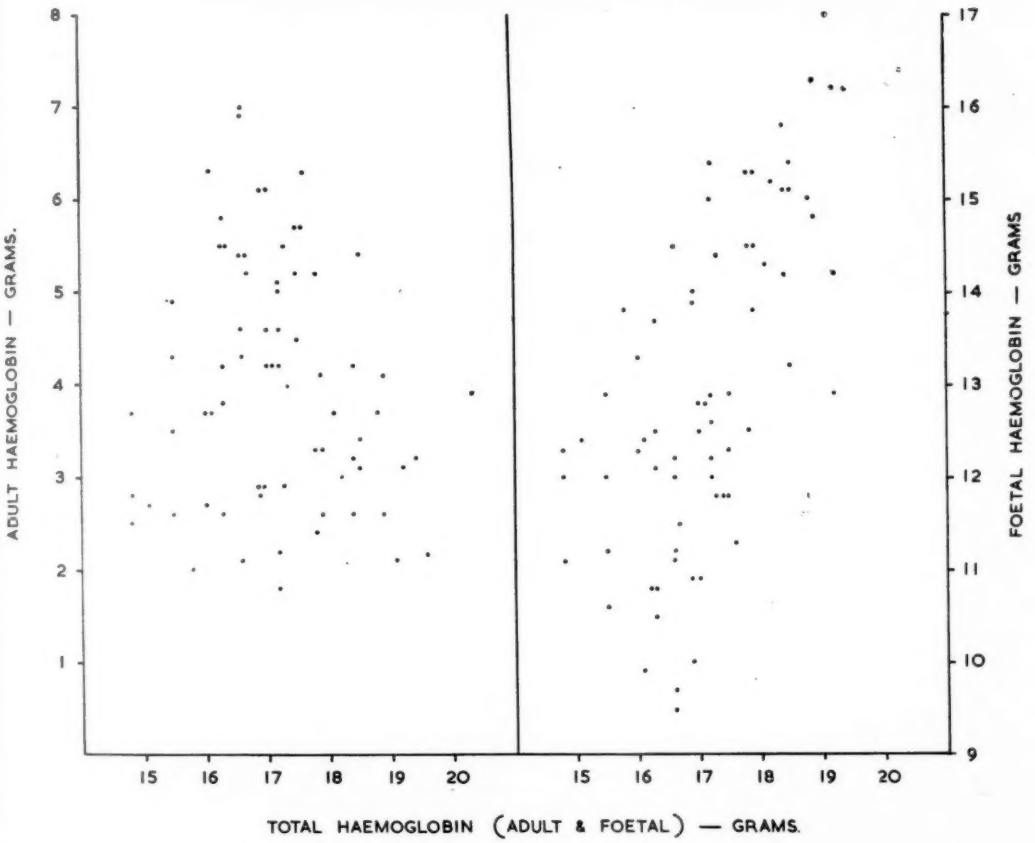
The regression equations of adult (A) and foetal (F) haemoglobin on menstrual age (W) and total haemoglobin (Hb) were calculated. The equations were:

$$A = \underset{\pm 0\cdot166}{0\cdot545}\ W \quad \underset{\pm 0\cdot150}{-0\cdot023}\ Hb \quad -17\cdot60$$

$$F = \underset{\pm 0\cdot165}{-0\cdot545}\ W \quad \underset{\pm 0\cdot150}{+1\cdot022}\ Hb \quad +17\cdot59$$

There is a highly significant ($P<0\cdot01$) effect of time on both adult and foetal haemoglobin, the former increasing and the latter decreasing as the foetus ages. When this effect is taken into account, differences in adult and total haemoglobin appear to be completely unrelated, but there is a highly significant ($P<0\cdot001$) regression of foetal haemoglobin on total haemoglobin (Fig. 2).

FIG. 2.—The correlation between foetal haemoglobin, adult haemoglobin and total haemoglobin when the foetal and adult haemoglobin levels are adjusted to eliminate the effect of gestational age.



These two equations strongly support the suggestion that, over the period 39 to 43 weeks, the amount of adult haemoglobin in each unit volume of the cord blood depends only on the age of the foetus, increasing as the foetus grows older. Although the amount of foetal haemoglobin normally decreases with increasing age of the foetus, the great increase in total haemoglobin (over 15 g.) which might be found at this stage in response to anoxia, arises entirely from an increase in the amount of foetal haemoglobin.

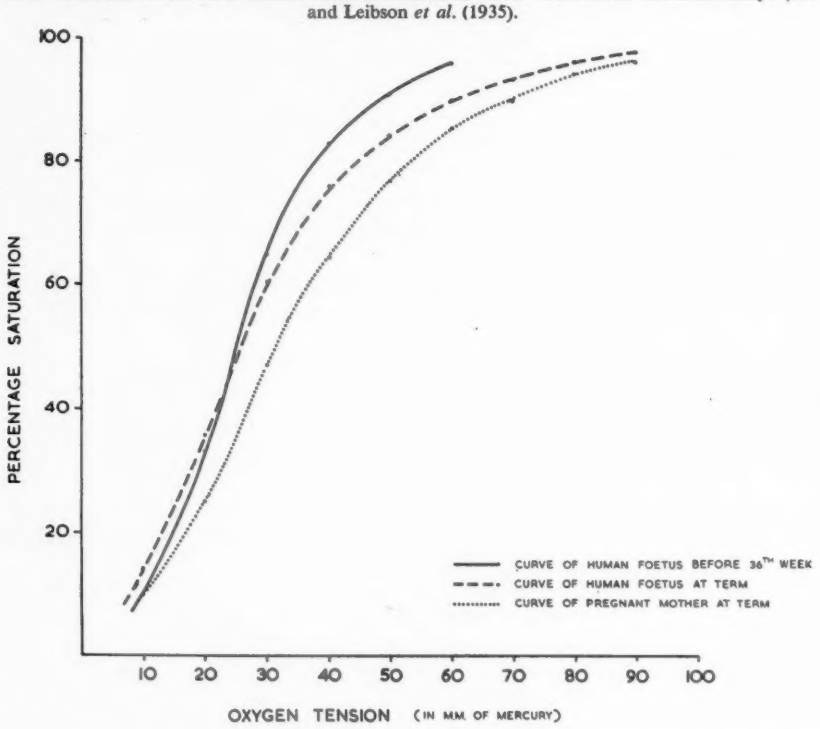
Discussion

The production of adult haemoglobin is part of the normal maturation of the blood. In the human foetus adult haemoglobin appears very early in gestation. The amount increases till at mid-pregnancy some 10% of the haemoglobin is of the adult type. It would appear from our findings and those of Schulman (1953) that up till the 35th or 36th weeks there is no great increase in production apart from the amount necessary to keep pace with increasing blood volume. After this time, however, adult haemoglobin increases greatly in amount and foetal haemoglobin production begins to decrease.

If, in the later weeks, the influence of anoxia is superimposed on the normal growth and maturation stimuli, extra haemoglobin is demanded and it would appear that this extra demand is met by the production of foetal haemoglobin. It would seem rational to suggest that such emergency supplies could best be obtained by maintaining production from centres producing foetal haemoglobin which normally would have been closing down, since adult haemoglobin centres are probably, at this time, already working at maximum capacity. This postulate assumes the existence of independent centres of production, perhaps side by side in each haemopoietic tissue or perhaps independent chemical processes existing side by side in the same centres.

Even though the method by which the foetus can rapidly obtain extra haemoglobin is not so simple as this, the production of extra foetal rather than adult haemoglobin by the anoxic foetus is physiologically advantageous. Under conditions of anoxia the haemoglobin level of the foetal blood rises. The main physiological result of this rise is to increase the gradient of pressure from the maternal to the foetal blood so that the oxygen content in the foetal blood may be maintained as near normal levels as possible despite a fall in the percentage saturation. If the increase in haemoglobin is achieved mainly by the production of foetal haemoglobin the gradient of pressure would be more easily increased because of a shift to the left in the dissociation curve of the foetal blood.

FIG. 3.—Dissociation curves of human foetal and maternal blood—from Sachs and Likhnizkaya (1938) and Leibson *et al.* (1935).



The Dissociation Curve. In Fig. 3 are shown the average oxygen dissociation curves of the blood of the human foetus up to the 36th week of pregnancy (Sachs and Likhnizkaya, 1938), of the blood of the human foetus at term, and of the blood of pregnant women at term (Leibson, Likhnitzky and Sax, 1936). Those curves have been selected for discussion in preference to those of Eastman, Geiling and De Lawder (1933) or Darling, Smith and Asmussen (1941), as all the curves shown were obtained by the same workers, under similar conditions, and probably represent the relationships more clearly.

We have shown that up till the 36th week only some 10% of the haemoglobin is adult in type, and the dissociation curve shown in Fig. 3 is well to the left of the curve of the blood at term (at least between 20 and 60 mm. oxygen pressure). At term, on average, 20% of the haemoglobin is adult, and the curve has shifted to the right so that, at 50% saturation, there is only half the gap between foetal and maternal curves that was between the curves before 36 weeks. It is interesting to note that Leibson *et al.* (1935) found that the curves in the blood of individual foetuses at term were not the same, and they actually suggested that 'the wide variation in the foetal dissociation curves lead us, however, to suppose that the foetal form of haemoglobin in the blood of the foetus before parturition has in different cases different qualitative and maybe quantitative significance'. The variation in the individual curves found by them could be explained by our finding of a great variation in amounts and proportions of foetal and adult haemoglobins in the blood of individual foetuses.

It would be interesting to study the dissociation curve of human foetal blood before the 20th week when little or no adult haemoglobin is present. It

appears, however, that when the proportion of adult haemoglobin rises after the 36th week the dissociation curve moves to the right and changes its shape, becoming more and more like the curve of normal adult blood and closer to the curve of the mother's blood. In the sheep, Barron (1951) found that the dissociation curve of the blood of the foetus begins to shift to the right and change its shape only after the 120th day, and Barron (1954) considers that the change in shape and position of the curve is due to the appearance at about 115 to 120 days and increased production of the adult type haemoglobin as shown by Karvonen (1949).

We have shown that under conditions of anoxia there is an increased production of foetal haemoglobin. Provided that such foetal haemoglobin is contained within foetal corpuscles, the effect would therefore be to cause the dissociation curve to shift to the left and alter its shape towards the early foetal position. The gradient of pressure from mother to foetus would therefore be improved at saturation over 40% (foetal) and oxygen pressures over 20 mm. mercury. Moreover, if the curve of Sachs and Likhnizkaya is correct in detail, transfer from the foetal blood to its own tissues would improve at saturation below 30%, both characteristics of the new curve being to the advantage of the foetus under deficient conditions of oxygen supply from the mother.

Effect on the Individual Foetus and Infant. *In utero* up till the 36th week the foetal blood can pick up oxygen easily, and at low capillary saturations transfer oxygen easily to its tissues. If, however, the infant is born much before the 36th week, nearly 90% of its haemoglobin is of the foetal type. Adult haemoglobin production lags behind for some weeks and foetal haemoglobin and cell production gradually cease, although a little more slowly than in the mature foetus (Jonxis, 1949; Schulman, 1953). The foetus is therefore certain to show a marked degree of anaemia in the first few weeks of life (Schulman, 1953), an anaemia which is very difficult to influence by iron therapy, as the ability to produce adult type haemoglobin is not yet adequately developed. In addition the dissociation curve of its blood is well to the left of that of the normal-term foetus and adult. Its blood can become saturated with oxygen easily, but there must be a very small gradient of transfer to its own tissues at the higher capillary saturations demanded by functioning tissues in an extra-uterine existence.

In the infant born after the 41st week of gestation two influences are very clearly at work. Adult haemoglobin is being formed in ever increasing amounts, but in view of the anoxia suffered by most of those infants there has been a marked rise in the haemoglobin level due mainly to an increase in foetal haemoglobin production. The summation of these opposite influences produces a blood with some 30% adult haemoglobin. The dissociation curve of the blood in the post-mature foetus and infant will therefore be much further to the right than that in the blood of the foetus at 40 weeks with the same haemoglobin level, as the post-mature foetus has much more adult haemoglobin. The blood of the foetus in the 42nd and 43rd week will therefore pick up oxygen much less easily from the maternal blood, but such a foetus, if born alive, will adapt much more easily to extra-uterine life and be more able to supply oxygen to its own tissues.

Relation of Haemoglobin and Red Cells. We have suggested that the dissociation curve of the blood of the foetus will vary in position and shape with the proportion of adult to foetal haemoglobin. We have suggested that the influx of extra foetal haemoglobin will be to the advantage of the anoxic foetus near term because of a consequent shift of the dissociation curve towards the early foetal position. The characteristic affinity for oxygen of foetal and adult blood depends entirely on the fact that the haemoglobins are contained within corpuscles (McCarthy, 1943), as there is no difference between the affinities of the haemoglobins themselves (Allen *et al.*, 1953). It seems clear, therefore, as suggested previously by Jonxis (1949) that foetal and adult haemoglobins are separately contained in foetal and adult corpuscles. It is interesting to note that, in Cooley's anaemia, in which the ability to produce adult haemoglobin is genetically absent, the cells are typically foetal in morphology. There is some indirect evidence from our findings to support the theory of distinct cell types. In a previous paper (Turnbull and Walker, 1954) we have shown that cells of the typical adult size (less than 7·5 μ) present in small numbers in the blood by the 10th week rise in number and proportion throughout pregnancy very like the changes in adult haemoglobin which we first detected at the 13th week. Gilmour (1941) has shown that definitive adult haemopoiesis is well established by this time. We have also shown previously that, in the latter weeks, foetal bloods with high haemoglobin levels have red cells of greater mean volume than bloods with normal haemoglobin levels, suggesting that the increase in haemoglobin promoted by anoxia, which we have shown to be achieved by the production mainly of foetal haemoglobin, is achieved by the production of extra red cells of greater volume, i.e., foetal cells.

We have found that in the blood of the foetus in the late weeks, some 35% of the cells are at least 9 μ in diameter, and we suggest that those cells along with some small cells are specific foetal cells containing foetal haemoglobin. The normal adult mean cell volume and mean cell diameter are reached only after some months of life, by which time cells over 9 μ have disappeared from the blood and true foetal haemoglobin is unlikely to be found in the blood of the normal infant (van Creveld, 1932; Jonxis, 1949).

Summary

The proportion of adult haemoglobin has been measured in the blood of the human foetus from the 10th to the 43rd week of pregnancy. Adult haemoglobin was first detected at the 13th week and rose until, at the 22nd to 24th weeks, 10% of the haemoglobin was adult. After the 35th week the proportion of adult haemoglobin rose steadily and at 42 weeks a mean value of 30·7% was found.

The rise in the proportion of adult haemoglobin is primarily a function of the growth and maturation of the foetal tissues, and in the well oxygenated foetus in the late weeks production of foetal haemoglobin steadily lessens.

The extra haemoglobin produced in the late weeks under the stimulus of anoxia is mainly or entirely of the foetal type.

Provided the two haemoglobins are contained separately in foetal and adult corpuscles, differences in the proportion of adult and foetal haemoglobins will greatly influence the position and shape of the oxygen dissociation curve of the blood. A shift to the left and a change in shape are greatly to the advantage of the anoxic foetus.

The effect clinically on the premature and post-mature infant is briefly indicated.

Further indirect evidence is submitted to support the theory that the two haemoglobins are contained in separate foetal and adult corpuscles.

We are greatly indebted to Dr. F. H. C. Marriot for all statistical analyses quoted in this paper; to Prof. Donald H. Barron for guidance in our discussion of the relation between the haemoglobins and dissociation curves; to Prof. Jonxis for advice on technique; and to other workers in this field who at the 19th Biological Symposium at Cold Spring Harbor were so generous with their advice.

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BLOOD FORMATION IN INFANCY

PART III*. CORD BLOOD

BY

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Blood taken from the umbilical vein at birth is of particular interest from two aspects. On the one hand it represents foetal blood at the end of gestation and may thus give information about influences acting on the foetus before birth. For example, the cord blood picture is now an accepted guide to the prognosis in haemolytic disease of the newborn (Mollison, 1951). On the other hand, cord blood represents the blood with which the infant begins extra-uterine life, so that it becomes of interest to enquire whether the blood picture at birth in any way determines the subsequent course of the blood picture.

There are several reports in the literature giving normal values for the various constituents of cord blood, but many relate only to small series and there are many discordancies. We have examined the cord blood from a large series of infants so that the wide range of the normal values can be taken into account.

Material and Methods

The subjects investigated were healthy infants born in the Cambridge Maternity Hospital. Umbilical vein samples were collected from 221 infants with birth weights above 2,500 g. and from 11 infants with birth weights less than 2,500 g. In every case pregnancy had been uncomplicated by toxaemia and labour had not been prolonged. Nitrous oxide-and-air analgesia had been given to the mothers.

The cord was clamped as soon as conveniently possible but usually some 10 to 15 seconds elapsed before this was done. The sample of blood was taken with a large-bore needle from the maternal end of the umbilical cord immediately after clamping. The specimens were examined by the haematological methods already described (Part I).

Particular attention was paid throughout to the accuracy of haemoglobinometry. Haemoglobin was determined as oxyhaemoglobin in a photoelectric colorimeter, using a blood dilution of one part in 200 parts of 0·04% ammonia. The colorimeter was checked each week against the Medical Research Council type of grey wedge photometer. A further check was made each month of both machines with iron determinations on several blood samples.

Results

The 221 samples were analysed for haemoglobin, and on 106 of them a full haematological examination was made. The results are shown in Tables 1, 2 and 3.

Haemoglobin. The results for the haemoglobin estimations were found to be distributed about the mean in the form of a normal curve. Calculation of the 95% range of normal was therefore feasible from a determination of the standard deviation. The mean of the results was 16·9 g./100 ml. and the 95% range 13·7–20·1 g./100 ml.

The results of the present series are compared in

TABLE 1

RESULTS OF Hb CONCENTRATION IN CORD BLOOD IN THE PRESENT SERIES COMPARED WITH THOSE OF OTHER AUTHORS

Author	No. of Observations	Mean	S.D.	Range
Mugrage and Andresen (1936)	40	17·1		13-20
Guest, Brown and Wing (1938)	34	17·9		13-22
Waugh, Merchant and Maughan (1939)	52	15·7*		12·2-19·0
Vahlquist (1941)	32	16·6	0·32	
De Marsh, Alt and Windle (1948)	60	16·0*		
Mollison (1951)	134	16·6	1·5	
Dochain, Lemage and Lambrechts (1952)	40	17·9		14·4-21·6
Present series	221	16·9	1·62	12·3-22·0

* Corrected as suggested by Mollison (1951).

* Previous parts were published in this journal: Part I (The Normal Bone Marrow), 1952, 27, 128; Part II (Normal Erythropoiesis), 1952, 27, 214.

Table 1 with those of other recent workers. In these recent studies, based on modern methods of haemoglobinometry, the results agree well.

Red Cells. For the red cell count, haematocrit, mean corpuscular haemoglobin and mean corpuscular volume, the results were found to fit normal distribution curves. In these, therefore, theoretical 95% ranges of normal may be calculated (Table 2).

TABLE 2

RED CELL VALUES IN CORD BLOOD

	Mean	S.D.	Calculated 95% Range
Haemoglobin (g./100 ml.) ..	16·9	1·62	13·7–20·1
Red cells (m./c.mm.)	5·09	0·78	3·5– 6·7
Haematocrit (%)	53·1	2·9	47·3–58·9
Mean corpuscular Hb (γγ) ..	33·5	1·48	30·5–36·5
Mean corpuscular vol. (c.μ) ..	104·2	7·0	90–118
Mean corpuscular Hb concentration (%)	32·3	—	30·9–36·5*
Reticulocytes (per 100 R.B.C.)	2·94	—	0– 8·3*
Normoblasts (per c.mm.) ..	590	—	0–5,400*

* Figues not represented by normal curve and extreme range of results given.

The macrocytosis previously noted by other workers has been confirmed, but the results show that the mean cell volume in about 25% of cord bloods will fall within the accepted range of normal for adult cells. These are, however, all on the upper side of normal as judged by adult standards. Only one determination was below 90 c.μ.

The values for mean corpuscular haemoglobin concentration were found not to follow a normal curve. The mean of the observations was 32·3% and the majority of the results lie above 32%. A small proportion of the results fall into the range 31-32%, but the stained film showed no hypochromia.

Reticulocytes. In the majority of infants the reticulocyte counts were above the normal adult values—in only 6% of the cases were the reticulocytes below 1%. The mean of the observations was 2·94% and although only a few of the infants showed values exceeding 5%, one showed a reticulocyte count of 8·3%.

Normoblasts were present in the majority of the specimens with a mean count of 590/c.mm. An occasional high value was found, the cord blood of three infants having normoblasts over 4,000/c.mm. None of the infants showing high normoblast counts showed other evidence of blood abnormality, nor was there any relationship between the normoblast count and the cord haemoglobin value.

Leucocytes. The values for the mean and the range of the leucocyte counts are shown in Table 3.

TABLE 3

LEUCOCYTE VALUES IN CORD BLOOD

	Mean	Range	95% Range
Leucocytes/c.mm.	12,900	5,900–26,000	6,000–22,000
Neutrophils juvenile % ..	0·7	0–4·0	0–3·0
juvenile/c.mm.	104	0–500	0–300
bands % ..	3·7	0–14	0–6
bands/c.mm. ..	464	0–2,100	0–1,200
segmented % ..	59·2	32–81	40–76
segmented/c.mm. ..	7,395	4,000–18,000	4,500–12,000
Eosinophils %	1·6	0–9	0–4·5
Eosinophils/c.mm.	230	0–1,100	0–800
Basophils %	0·25	0–2·5	0–1·5
Basophils/c.mm.	38	0–350	0–200
Lymphocytes %	26·2	9–47	13–40
Lymphocytes/c.mm. ..	3,245	900–9,500	1,000–6,000
Monocytes %	6·08	0·5–16·0	2–12
Monocytes/c.mm.	731	150–2,800	200–1,600

The results do not follow normal curves, so that theoretical ranges cannot be calculated. In the majority of the estimations, however, it has been possible to give a range which would cover about 95% of normal subjects.

In cord blood all the cell types are present in increased numbers, but in proportions similar to those of adult blood. The leucocytosis is thus a general rise and not the neutrophil leucocytosis which is quoted in many textbooks. The error appears to have arisen because it has usually been assumed that cord blood and blood sampled a few hours after birth are equivalent. In Part I it was shown that during the first few hours there was a rise in neutrophils while the lymphocytes remained unchanged.

Discussion

Relationship of Cord Haemoglobin Level and Foetal Maturity. The wide spread of the haemoglobin values, from 12 to 22 g./100 ml., raises the question whether the more extreme values are still to be accepted as normal. According to Walker and Turnbull (1953) the normal cord blood haemoglobin level varies relatively little. These authors found the haemoglobin level of the foetal blood tended to rise throughout pregnancy, and at 40 weeks' gestation averaged 16·5 g. (agreeing with our mean value of 16·9) with a range of 15·0 to 18·6. They considered higher values as implying that some degree of more or less prolonged hypoxia had been

suffered by the foetus, and stressed that post-maturity was associated with abnormally high haemoglobin values: at 43 weeks' gestation, for instance, the range was 16·8-20·5 g. From their findings Walker and Turnbull concluded that post-maturity leads to placental insufficiency, a conclusion which would be in accord with what is known about post-maturity in experimental animals.

In view of the obvious importance of this theory, should it be confirmed, we have checked our data on menstrual age and birth details carefully, but without finding the least suggestion of correlation between maturity and cord blood level (Fig. 1). Cord blood haemoglobin was also plotted against crown-heel length and against birth weight, two other possible yardsticks of foetal maturity, but in neither instance was any correlation found.

In addition we have scrutinized the nine cases of our series in which the cord blood haemoglobin was 20 g. or higher, values which, according to Walker and Turnbull, are to be found only in circumstances where post-maturity or other abnormalities causing foetal hypoxia are present. Details of the cases are set out in Table 4. In addition to the details recorded in Table 4, the existence of abnormalities of pregnancy or labour was sought, such as clinical signs of post-maturity, maternal diabetes, toxaemia, prolonged or difficult labour, Caesarean section, foetal distress or previous history of miscarriages. None of these abnormalities was found.

TABLE 4

BIRTH WEIGHT, MENSTRUAL AGE, AND LENGTH OF NINE INFANTS WITH CORD HAEMOGLOBIN VALUES OF 20 g./100 ml. AND HIGHER

	Haemo-globin (g./100 ml.)	Birth Weight		Menstrual Age ± 280 Days	Length	
		(lb. oz.)	(g.)		in.	(cm.)
1	20·0	8 0	3,630	− 2	—	—
2	20·0	7 4	3,290	− 2	—	—
3	20·0	9 6	4,226	− 4	22	56
4	20·1	6 8	2,952	?	19	48
5	20·2	6 5	2,860	? +18	18½	47
6	21·0	5 12	2,620	− 5	19	48
7	21·2	7 2	3,234	+ 4	—	—
8	22·0	8 1	3,650	− 7	22	56
9	22·0	7 9	3,430	+ 4	21	53

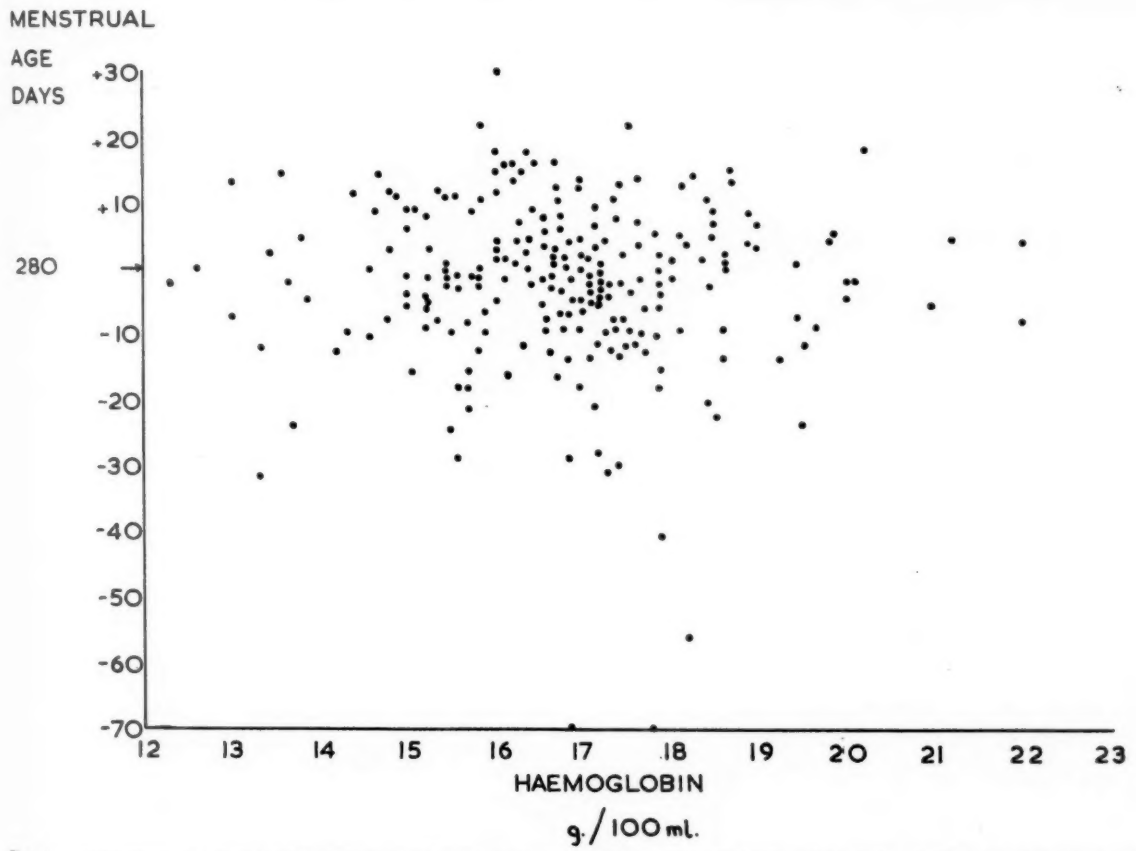

FIG. 1.—Scattergram of haemoglobin values of cord blood from 232 infants (11 with birth weights below 2,500 g.) against menstrual age expressed as days greater or less than 280 days to show absence of any correlation between cord blood haemoglobin level and foetal maturity.

Our results thus argue against the view that postmaturity or other abnormality of pregnancy is common in cases with high cord haemoglobin. The menstrual age of our 232 infants varied from 70 days premature to 30 days post-mature, with quite as wide a variation as in the smaller series of Walker and Turnbull. At present we can offer no explanation of the divergence between our results and theirs.

Relationship between Haemoglobin Concentration at Birth and at 7 and 9 Weeks. The wide spread in the normal concentration of the haemoglobin at birth prompted a second question: Does the extent to which the haemoglobin level falls during the first three months depend upon the haemoglobin level at birth?

During the first eight weeks of life the haemoglobin concentration of the infant falls to an average value of about 11 g./100 ml., due to a physiological hypoplasia of the bone marrow (see Part II). The precise level at which the haemoglobin level stabilizes at this time does show some variation: this might be due to variations in the initial count at birth. To test this possibility 19 infants were examined at 7 weeks and 9 weeks after birth: 11 of these had low normal cord haemoglobin values (13·0–15·0 g.) and eight had high normal cord haemoglobin values (18·4–20·1 g.). The results are shown in Table 5. There is no significant difference between these two groups of infants 7 and 9 weeks after birth. Both in the low and high cord haemoglobin groups an occasional infant showed a drop in haemoglobin value to below 10 g. at the seventh week after birth.

These results show that whether an infant is born with a cord blood haemoglobin as low as 13 g. or as high as 20 g. the haemoglobin will have stabilized at a level of about 11 g. at 2 months of age.

TABLE 5

HAEMOGLOBIN VALUES AT 7 WEEKS AND 9 WEEKS OF INFANTS BORN WITH HIGH OR LOW CORD HAEMOGLOBIN VALUES

Cord Blood Haemoglobin (g. %)	No. of Cases	Mean Hb (g. %) (and Range) at 7 Weeks	Mean Hb (g. %) (and Range) at 9 Weeks
'High' (18·4-20·1)	8	11·5 (9·1-12·8)	11·5 (10·6-14·0)
'Low' (13·0-15·0)	11	11·6 (9·1-13·9)	11·8 (10·9-12·9)

Summary

From analyses of cord blood from a large series of infants normal haematological values have been derived.

The normal cord blood haemoglobin level ranges from 12 to 22 g. No relationship between cord blood haemoglobin and foetal maturity was found.

The haemoglobin level at 7 weeks and 9 weeks of age was determined in two groups of infants, (*a*) those born with a high normal cord haemoglobin and (*b*) those born with a low normal cord haemoglobin. At 2 months of age each group had a similar haemoglobin level of about 11 g./100 ml.

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THE USE OF COBALT IN SOME COMMON ANAEMIAS OF CHILDHOOD

BY

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In view of the unsatisfactory response to iron of certain common anaemias in childhood, it was decided to treat a series of cases with cobalt to find out if this substance would prove a satisfactory substitute for iron in refractory cases. Fifty cases were treated, and all had types of anaemia usually showing a poor response to iron, liver and other haemopoietic agents in common use. There were 31 cases of anaemia associated with infection, 10 were anaemic premature infants and three were cases of rhesus incompatibility after the need for transfusion had passed but which showed a residual anaemia. There was one case of severe physiological anaemia and one which developed anaemia after a Rammstedt's operation, although there was no evidence of gastric haemorrhage. The remaining cases comprised twins with a fairly severe anaemia of unknown aetiology and a case of erythrogenesis imperfecta which is included out of interest in spite of the baby's failure to respond to cobalt.

The Anaemia of Infection

The anaemia associated with infection is characterized by a normochromic, normocytic blood picture with a colour index of around 1. Microcytosis is occasionally seen but is not accompanied by hypochromia (Saifi and Vaughan, 1944). The anaemia is rarely severe except in cases of long-standing suppuration, but is a considerable problem in childhood as it is resistant to treatment by ordinary haemopoietic agents, favours the development of further infection and may retard convalescence. Evidence of blood regeneration is slight and the reticulocytes are normal or reduced (Kugelmass and Lampe, 1932; Wintrobe, 1951). Saifi and Vaughan (1944), however, found well marked reticulocyte responses in their series of cases with chronic infections, though this was less marked in those with recent acute infections. They found no evidence of increased blood destruction in cases of anaemia associated with infection.

The 31 children with anaemia secondary to infection ranged in age from 2 months to 7 years, with an average of 1 year 5 months. Any cases where the aetiology was in doubt or who were known to be anaemic before infection were excluded from the series. The infections were of all types seen in an acute children's ward, with a predominance of otitis media and bronchopneumonia.

The pre-treatment haemoglobin levels averaged 62·4% (Haldane 14·8 g. = 100%), 9·23 g., and the red cell counts averaged 3·92 million per c.mm. The average colour index before treatment was 0·80.

The red cells before treatment usually appeared normal on the stained film but occasional microcytosis and anisocytosis was seen. This, however, was never a marked feature. All cases had a full blood count before treatment was instigated, haemoglobin and red cells were estimated weekly during the period of treatment and the white cells were counted again at the end of treatment. No cases received iron during the period of cobalt therapy. In the majority of cases, the duration of treatment was three weeks, two cases were treated for six weeks, and three made such satisfactory progress that treatment was stopped after two weeks. Cobalt sulphate was given orally in all cases; the dosage was 25 mg. daily in 22 cases, and 20 mg. daily in the remaining nine cases.

Results. The results of treatment are expressed in the total rise of haemoglobin and red cells over each week of treatment and are shown in Table 1. In the two patients in whom treatment was continued for more than three weeks, the figures for the first three weeks only are included in Table 1. From Table 1 it is apparent that the greatest rise in both red cells and haemoglobin occurred during the first week of treatment. In the second week the

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increases were much less marked but during the third week greater rises were again shown though these did not equal those of the first week. Some of the cases were treated on admission, others, if the blood levels were satisfactory at that time, did not receive cobalt till later in the infection. The average count, at the end of three weeks' treatment, showed a rise of 13·6% haemoglobin (2·01 g.) and 0·83 million red cells. There were no toxic effects in any case.

TABLE 1
RESPONSE OF 31 CHILDREN WITH ANAEMIA SECONDARY TO INFECTION

	Haemoglobin	Red Blood Cells (m.)	Colour Index
Average initial count ..	62·4% 9·23 g.	3·92	0·80
Average final count ..	76·0% 11·24 g.	4·75	0·83
Average rise over weeks:			
(I)	7·9% 1·16 g.	0·48	
(II)	3·1% 0·45 g.	0·19	
(III)	4·6% 0·68 g.	0·24	

Dosage { 25 mg. daily in 22 cases.
20 mg. daily in 9 cases.

Results. The results of therapy are shown in Table 2. The cases showed a gradual falling off in the response of both haemoglobin and red cells during the three weeks of treatment as normal blood levels were approached. The results on the whole were more satisfactory in the premature infants than in the cases of infection. This was particularly marked in the rise of haemoglobin and is possibly related to a difference in the mode of action of cobalt in the two series which will be discussed later.

TABLE 2
RESPONSE OF NINE PREMATURE INFANTS

	Haemoglobin	Red Blood Cells (m.)	Colour Index
Average initial count ..	62·0% 9·17 g.	2·96	1·07
Average final count ..	83·0% 12·28 g.	3·81	1·11
Average rise over weeks:			
(I)	9·3% 1·37 g.	0·48	
(II)	7·5% 1·11 g.	0·33	
(III)	5·8% 0·85 g.	0·06	

Dosage: 20 mg. daily.

The Anaemia of Prematurity

The anaemia of prematurity resembles the anaemia associated with infection in that it is a normochromic normocytic anaemia with little evidence of blood regeneration. After three to four months, iron deficiency plays an increasing part in the pathogenesis of the anaemia and hypochromia and microcytosis become evident. Before this age, however, there is little to suggest that iron deficiency is of importance in the aetiology, and the early anaemia fails to respond to iron. Nine cases of the anaemia of prematurity were treated satisfactorily with cobalt. The nine premature infants had birth weights ranging from 2 lb. 1 oz. to 4 lb., with an average of 3 lb. 3 oz. The average age of starting treatment was 10 weeks with a range of 7 weeks to 16 weeks. The maximum degree of anaemia of prematurity occurs from 10 to 14 weeks (Mackay, 1935; Lichtenstein and Nordenson, 1939). These children, therefore, were treated at the height of the anaemia at a time when little response to anything but blood transfusion was to be expected. All cases were treated for three weeks, and the dosage was 20 mg. cobalt sulphate daily, given by mouth. No cases received iron during the period of cobalt treatment, the drug was taken well in all cases, and there were no toxic effects.

A tenth case, J.T., a premature twin of birth weight 3 lb., was seen at the age of 4½ months when his haemoglobin was 70% and red blood cells 2·54 million. In view of the high colour index and a normal film, he was started on cobalt, 20 mg. daily, and one week later the haemoglobin remained at 70%, though the red cells had risen to 2·8 million. After a further week the haemoglobin had fallen to 64% and the red blood cells were 3·1 million. At this stage an iron deficiency was obvious and ferrous sulphate, grains 4½ daily, was introduced in addition to the cobalt. After a further week the haemoglobin was 78% and red cells 3·62 million, and the cobalt was discontinued. The average colour index before treatment was 1·07 and after treatment 1·11, an indication that the iron supplies of these infants were sufficient to meet the demands of increased haemopoiesis.

Miscellaneous Anaemias

The eight cases which responded to cobalt are shown in Table 3. Because of the variations in age and type of anaemia, no effort has been made to average the results; the initial counts, final counts and rise over the period of treatment are given. All cases, except J.G., received iron at the same time, but as all had been treated with iron for a minimum of three weeks previously with no response, it is

TABLE 3
MISCELLANEOUS ANAEMIAS SHOWING RESPONSE TO COBALT

Name	Age	Diagnosis	Initial Count		Final Count		Rise over Period of Treatment		Duration (Weeks)
			Hb (%)	R.B.C. (m.)	Hb (%)	R.B.C. (m.)	Hb (%)	R.B.C. (m.)	
G.L.	3 months	Rhesus incompatibility	54	2·96	84	5·21	30	2·25	3
C.B.	3 months	Rhesus incompatibility	54	3·50	87	5·0	33	1·5	5
A.W.	4 months	Rhesus incompatibility, marasmus, collapse of left lower lobe	66	3·50	74	4·32	8	0·82	8
K.S.	1 month	Cord haemorrhage	58	3·02	87	3·57	29	0·55	4
S.M.	7 weeks	Pyloric stenosis, Rammstedt's operation	61	3·42	80	4·54	19	1·12	7
C.H.	2 months	Physiological anaemia	61	3·06	86	5·64	27	2·58	6
P.G.	5 weeks	Anaemia ? cause	74	3·84	91	5·08	17	1·24	4
J.G.*	5 weeks	Anaemia ? cause	62	2·84	109	6·10	47	3·26	4

* No additional iron.
Dosage: 25 mg. daily.

unlikely that this was responsible for the satisfactory results. The least satisfactory response occurred in A.W., an infant with erythroblastosis foetalis who, after an exchange transfusion at birth and a later simple transfusion, remained persistently anaemic, marasmic without obvious cause, and just before cobalt treatment was introduced developed a complete collapse of the left lower lobe due to upper respiratory infection. There were thus probably three factors in the production of the anaemia; infection, failure of nutrition, and erythroblastosis, although at 4 months it is unlikely that haemolysis was still active.

The twins, P.G. and J.G., presented an interesting anaemia, the aetiology of which was never established. Born at 38 weeks, with birth weight 7 lb. 15 oz. and 5 lb. 1 oz., the mother had a severe toxaemia and later developed agranulocytosis for which no cause was found. She was not, however, anaemic during her pregnancy.

The infants, who were never breast-fed owing to the maternal condition, were noted to be pale during the first week of life and at 4 days had haemoglobin of 66% and 58% respectively. Iron was given at once, without effect. At the age of 5 weeks, both infants developed mild respiratory infections and were admitted to hospital. No increased haemolysis was detected, the Coombs test was negative, and the bone marrow of both infants was within normal limits. The iron was discontinued in the second twin when cobalt was begun in order to assess if cobalt alone could prove effective; in fact this baby did considerably better than his brother and developed a polycythaemia.

The last case, D.S. (Fig. 1), of hypoplastic anaemia of the type described by Diamond and Blackfan (1938), was included because of the failure to respond to cobalt. This child had had repeated transfusions over a period of years in addition to all the commonly used haemopoietic agents. Marrow studies confirmed the diagnosis with normal cells of the granulocyte series and only 4·0% total erythroid precursors. The only response obtained in his case was a reticulocytosis of 1·2% on the second day of treatment. This was not maintained and doubling the dose to 100 mg. daily had no

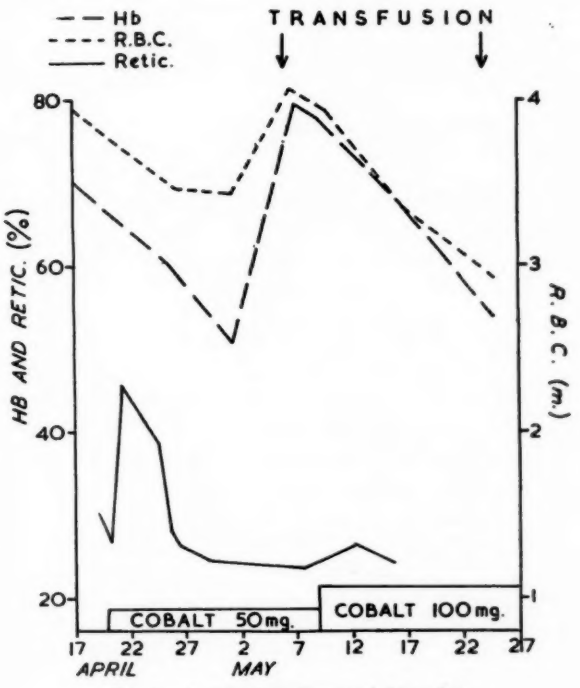

FIG. 1.—A case of erythrogenesis imperfecta.

effect. Diamond and Blackfan (1938) tried iron and cobalt in their four cases without success. Cathie (1950), who suggested the name of erythrogenesis imperfecta for such cases, stated that blood trans-

fusion was the only satisfactory method of treatment; cobalt was among the drugs tried in his series of five cases. Seaman (1952), however, reported a child kept alive for 10 years with transfusions who developed reticulocytosis and normal erythropoietic tissue in the marrow after treatment with cobaltous chloride. There was no effect following cobalt in a case of congenital hypoplastic anaemia. Encouraging results have been obtained from cobalt therapy in cases of acquired erythrogenic hypoplasia in both adults and children (Seaman and Koler, 1953; Rohn and Bond, 1953) and it is felt that cobalt is worthy of trial in cases of erythrogenesis imperfecta, despite the unsatisfactory results in the case reported here.

Mode of Action of Cobalt

The mechanism of cobalt in the therapy of anaemia is unknown and further studies were undertaken in some patients in an effort to elucidate this. Twelve cases had marrow punctures before and after cobalt treatment. Six were cases of anaemia with infection and six were premature infants. All these cases responded satisfactorily as far as the peripheral blood was concerned. Nine cases showed a rise in the total erythroid precursors in the marrow, associated with a fall in the myeloid/erythroid ratio. In two cases the levels were approximately the same before and after treatment, and in one case, P.F., the erythroid precursors showed a marked fall after treatment. This was a child of 6 years with miliary tuberculosis who was under treatment with streptomycin and P.A.S. Cobalt in this case was continued for six weeks, and it is possible that the prolonged treatment was responsible for these marrow changes. This would agree with the work of Davis, McCullough and Rigdon (1945) on ducks, which showed a marrow hyperplasia up to the fourteenth day of cobalt treatment, but by the nineteenth day the marrow had become hypoplastic. This was correlated with a decreased proportion of young cells in the peripheral blood though the total counts remained high. It is of interest to note in P.F. that, after an initial rise in both red cells and haemoglobin during the first three weeks of treatment, the haemoglobin remained stationary and the red cells showed a slight but definite fall. After cobalt was discontinued, however, the counts remained satisfactory and there was no evidence of permanent depression of the marrow. The granulocyte series appeared unaffected by this hypoplasia.

Erythroid marrow hyperplasia suggests that one action of cobalt is a direct stimulation of the marrow erythroid tissue. Similar changes in the erythroid tissue after treatment have been noted by Weissbecker (1950), Wolff (1950), Virdis (1952), Gardner (1953) and Schmöger (1953).

This stimulation is possibly temporary, and if cobalt is continued may give place to a depressant action on the marrow. Table 4 shows the average initial levels for the marrow erythroid series. Here the cases are divided into premature infants and those with infections, and the differences between the two groups of children are most marked in the oxyphilic or late normoblastic series. Table 4 also shows the proportional rise over the initial levels in the various groups. Again, the differences between premature babies and infection cases is most marked at the oxyphilic level. The premature infants showed a rise of 79·1% at this level, the cases of infection a fall of 7·1% of initial values. The basophilic normoblasts and pro-erythroblasts also showed a marked difference in the reaction of the two groups. The premature infants showed a fall of 6·8% of the initial value, the cases of infection a rise of 22·1%. These figures suggest that cobalt may act differently in the two groups of cases. Stimulation of the late normoblastic series in the premature infants suggests a favourable influence on iron utilization. This would link up with the fact that iron supplies appear adequate in the early anaemia of prematurity and suggests a functional inability to utilize iron for haemopoiesis rather than marrow depression in these infants. This is supported by the work of Lichtenstein and Nordenson (1939) on the bone marrow of premature infants. These authors found no evidence of marrow depression, but rather, an active though immature marrow. It is pointed out by Rohn, Bond and Klotz (1953) that total haemoglobin cannot exceed that represented

TABLE 4

PRE-TREATMENT LEVELS FOR MARROW ERYTHROID SERIES AND PROPORTIONAL RISE OVER INITIAL VALUES AFTER TREATMENT

	Initial Average Levels for Erythroid Series		
	All Cases	Premature Infants	Infections
Total erythroid rise (%) ..	21·5	20·6	22·4
Pro-erythroblast and basophil normoblasts (%) ..	6·81	6·5	6·94
Polychromatic normoblasts	10·47	11·0	9·94
Oxyphilic normoblasts ..	4·31	3·04	5·25
	Proportional rise over initial values		
Total erythroid rise (%) ..	16·2	22·7	10·2
Pro-erythroblast and basophil normoblasts (%) ..	15·7	6·8 Fall	22·1
Polychromatic normoblasts	19·2	23·4	15·4
Oxyphilic normoblasts ..	25·1	79·1	7·1 Fall

by normochromia of the cells available, so that ultimately the cell count is the limiting factor in the blood picture. As our series of premature babies had a colour index of 1·07 before treatment, it is possible that the initial action of cobalt in all cases is stimulation of red cell production, and in the premature infants the increased utilization of iron is merely secondary to the increased demands of the marrow. After the initial stimulation the action of increased iron utilization may then play the major part in these cases, whereas in the children with infection the direct stimulating action continues to predominate. The premature infants show a rapid rate of growth and presumably their iron demands are in excess of those of children whose blood volume is increasing less quickly and who, once normal blood levels have been reached, have merely to maintain equilibrium. This may also perhaps explain the greater rise in total erythroid precursors seen in the premature infants, 22·7% over initial figures, compared to a rise of 10·2% in the cases of infection. The marked increase in the early erythroid cells in the cases with anaemia of infection point to a direct stimulation of the erythroid tissue of the marrow as the main action of the cobalt. This double action of cobalt also seems likely from the work of Kato and Iob (1940). They found marrow hyperplasia of cell elements, particularly of the erythroid series after cobalt administration, and also found less iron storage in the spleen and marrow when cobalt was given with iron than when iron was given alone, thus suggesting that cobalt enhanced iron utilization.

TABLE 5

RETICULOCYTE RESPONSE AFTER ONE, TWO AND THREE WEEKS' TREATMENT WITH COBALT

Week of Treatment	Average Reticulocyte Response (%)	
	Premature Infants	Infections
1	3·4	2·3
2	2·3	1·8
3	1·5	1·6

It is realized that no conclusions can be drawn from so few cases but these figures seemed sufficiently striking to suggest a possible dual mechanism for the action of cobalt in anaemia.

These 12 cases also had reticulocyte counts at the end of one, two and three weeks' treatment. The average reticulocyte count before treatment was 0·7%; the counts after treatment are shown in Table 5. The responses obtained were not dramatic, the maximum response being 4·7% at the end of one week, and the premature infants showed rather higher levels than the cases with infection. Robinson, James and Kark (1949) obtained maximum responses in their cases between the sixth and tenth days of treatment, but in no case did the reticulocytes exceed 5%. It is possible that in this series the peak of reticulocytosis was missed, owing to the infrequent examinations, but the findings are in agreement with those of most authors who feel that the reticulocyte responses found after cobalt therapy are not sufficiently marked or consistent to provide a reliable guide to the efficiency of treatment (Rohn *et al.*, 1953; Gardner, 1953; Quilligan, 1954). Some German authors, however (Wolff, 1950; Schmöger, 1953), have reported responses of up to 80%. It is possible that in their series a different technique was used in the estimations.

Examination of peripheral blood films before treatment showed normal red cells in most cases. Occasional hypochromia was present but this was never a marked feature. Polychromatic and nucleated red cells were not seen before treatment. After treatment, however, polychromasia became fairly marked and occasional normoblasts appeared in the films. In the premature infants this was particularly marked. At no time during treatment did hypochromia become marked except in the premature twin, J.T., previously described. This suggested that endogenous iron supplies were adequate in these children. It is felt that if in the course of treatment hypochromia becomes apparent or haemoglobin production lags behind red cell increases, iron should be given in addition.

Summary and Conclusions

Fifty cases of anaemia in childhood were treated with cobalt and satisfactory results were obtained in all but one case. All had types of anaemia usually resistant to iron therapy.

Marrow studies before and after treatment showed an erythroid hyperplasia in nine of 12 cases.

Reticulocytosis was not marked in the children studied. There were no toxic effects in the dosage used.

The possible mode of action of cobalt in the therapy of anaemia is discussed.

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THE DETERMINATION OF BLOOD PRESSURE IN INFANTS BY THE FLUSH METHOD

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Accurate determination of the blood pressure in the arms of small infants by auscultation, and even by palpation, is a difficult and time-consuming procedure. For this reason it is either not attempted, or, if it is, the results are liable to be inaccurate. It is usually impossible to obtain blood pressure readings in the legs by these methods at this age. The need for a simple and accurate method is evident and we believe that the flush method described below provides it. Goldring and Wohltmann (1952) have shown that this method gives readings about 10 mm. Hg lower than the auscultatory method, and this has been our experience also in older children where the comparison can be made. The purpose of this paper is to make this technique more widely known; in it we describe the findings obtained in normal infants, show the variation of the method, and establish the gradient of systolic blood pressure between the arms and legs in normal infants. Readings from two cases of coarctation of the aorta are included to demonstrate the value of the method in the early diagnosis of this condition in infancy.

The Method

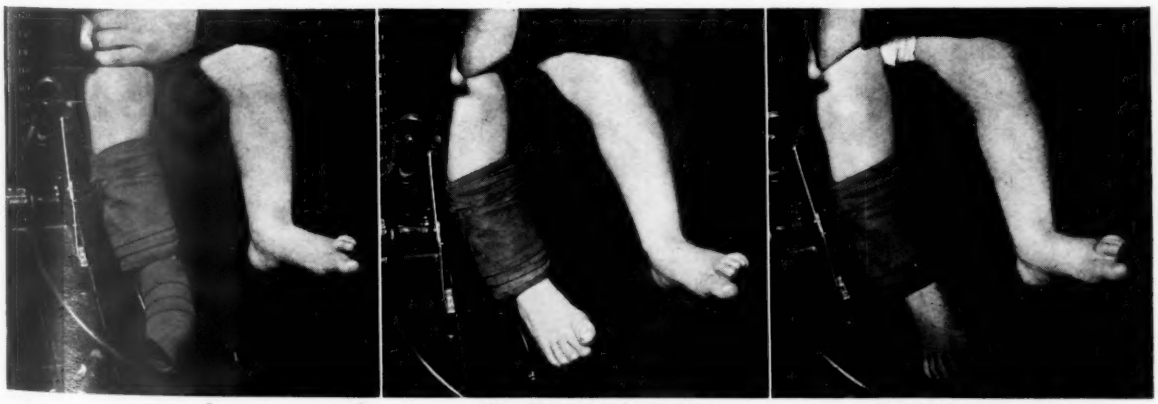
The method is based on that originally described by Gaertner (1899) for determining digital blood pressures. He used an inflatable cuff placed round the base of the finger and connected to a manometer.

A blood pressure cuff of the appropriate size is placed round the forearm or lower leg of the infant. The limb distal to the cuff, which must be warm, is then exsanguinated by wrapping a thin sheet rubber or crepe bandage around it from the periphery up to the level of the cuff. The cuff is inflated to well above the expected systolic pressure and the bandage is removed. The pressure in the cuff is then slowly released by an assistant, while the observer watches closely, in a good light, for the first signs of a flush as blood re-enters the exsanguinated limb (Fig. 1). Provided the limb is warm and has been blanched completely, and if the pressure is released not faster than 5 mm. per second, this end-point is abrupt and quite distinct. It must be emphasized that it is the first sign of flushing that is taken as the point of systolic pressure.

It is essential that the baby should be quiet, neither crying nor moving the limbs excessively.

Woodbury, Robinow and Hamilton (1938) have shown, using intra-arterial pressure recordings from the umbilical artery in 10 normal infants, that the average rise in systolic pressure on crying was 27 mm. Hg. We have found a bottle feed or a teat filled with glucose solution an effective method of sedation.

The correct width of cuff is of importance. We have found that the 2·5 cm. cuff as recommended by some (Goldring and Wohltmann, 1952) gives very variable



I II Exsanguinated III Showing flush

FIG. 1.

results by this method, and we have discarded it in favour of the 6 cm. cuff for small infants. It has been suggested (Woodbury *et al.*, 1938) that this size of cuff gives too low readings, but it will be seen that our results in newborn infants by this method compare quite well with the mean figure of 64 mm. Hg obtained by direct recordings from the umbilical artery by Abt and Feingold (1930). Where possible two recordings should be taken from each limb.

Variation of the Method

Sixteen readings of systolic blood pressure from the right leg were made in each of five normal newborn infants (Table 1). In each subject, all the readings were obtained within a period of 12 hours. It was not possible to complete each investigation at one time as the infant tended to become restless if more than four readings were made consecutively.

TABLE 1
SYSTOLIC BLOOD PRESSURES FROM RIGHT LEG IN FIVE NORMAL INFANTS

Readings (mm. Hg)	Infant 1 (2 Days Old)	Infant 2 (1 Day Old)	Infant 3 (2 Days Old)	Infant 4 (1 Day Old)	Infant 5 (3 Days Old)
1	56	56	48	48	50
2	58	62	48	48	48
3	58	56	48	46	50
4	60	60	46	46	54
5	50	52	52	38	58
6	46	50	58	40	56
7	50	50	50	42	64
8	48	54	56	40	58
9	46	56	48	40	40
10	46	60	54	42	44
11	50	56	50	40	44
12	50	60	52	40	48
13	54	54	46	40	50
14	56	60	52	42	48
15	56	60	48	40	52
16	48	62	48	44	58
Mean ..	52	57	50	42	51
Standard error of the mean	1·2	0·97	0·85	0·78	1·5

It will be seen that the standard error of the mean in these five subjects varies between 0·78 and 1·5.

Systolic Blood Pressure in Arms and Legs in Normal Newborn Infants

Sixteen infants in the neonatal period are included in this investigation and two readings have been taken from each limb. The results are shown in Table 2.

In this group the systolic blood pressure in the legs was lower than that in the arms in all but two instances. In the majority this difference ranged between 1 and 5 mm. Hg and in none was the leg systolic pressure more than 13 mm. lower than that in the arms.

It has been stated (Woodbury *et al.*, 1938) that, in the first 10 days of life, the systolic blood pressure of the infant gradually rises. Our figures (Table 2) confirm this observation.

TABLE 2
SYSTOLIC BLOOD PRESSURE IN ARMS AND LEGS IN NEONATAL PERIOD

Age	Case	Arms (mm. Hg)		Legs (mm. Hg)	
		Right	Left	Right	Left
1st day	(1) C.K.	46	48	57	58
		50	50	60	58
	(2) B.B.	54	52	60	55
		58	50	58	56
	(3) B.T.	61	56	54	51
		60	60	56	55
	(4) A.C.	50	54	51	50
		55	54	50	50
4th day	(5) W.C.	66	68	64	60
		66	66	64	64
	(6) R.A.	68	66	56	54
		65	64	57	54
	(7) B.H.	68	62	58	66
		69	66	60	66
	(8) B.L.	66	66	67	65
		66	70	64	66
7th day	(9) R.S.	58	61	58	55
		62	64	56	57
	(10) Y.M.	76	78	71	74
		75	78	69	74
	(11) S.K.	64	64	68	66
		71	68	72	58
	(12) C.S.	70	66	58	54
		65	66	60	60
11th day	(13) K.N.	75	74	71	70
		79	74	76	70
	(14) R.D.	77	73	69	67
		80	79	61	70
	(15) R.Y.	67	69	64	66
		71	69	64	68
	(16) D.D.	76	74	65	67
		76	70	68	67

Systolic Blood Pressure in Arms and Legs of Older Infants

Eleven infants were investigated in this group and the findings are shown in Table 3.

TABLE 3
SYSTOLIC BLOOD PRESSURE IN ARMS AND LEGS IN NORMAL INFANTS

Age	Case	Arms (mm. Hg)		Legs (mm. Hg)	
		Right	Left	Right	Left
2 months	(1) B.H.	100	104	98	103
		103	108	98	95
3 months	(2) E.K.	85	85	96	83
3 months	(3) B.T.	100	102	105	110
		98	98	98	110
4 months	(4) R.H.	110	112	99	104
		112	114	96	105
4½ months	(5) T.S.	80	80	74	72
		83	82	78	74
6 months	(6) B.S.	75	78	78	78
		80	80	79	82
7 months	(7) C.K.	86	88	75	85
8 months	(8) R.W.	100	88	92	98
		102	94	96	102
13 months	(9) M.T.	98	90	110	100
		98	94	116	102
15 months	(10) B.R.	92	101	96	110
2½ years	(11) W.R.	102	98	108	100
		106	96	110	103

In this group the systolic blood pressure in the legs was higher than that in the arms in five subjects, and three of these are the three oldest children included in this investigation. In no instance was the systolic pressure in the legs more than 14 mm. Hg lower than that in the arms.

Flush Blood Pressure Readings in Coarctation of the Aorta

The blood pressures in two cases of coarctation of the aorta (adult type) in infants are shown in Table 4 to illustrate the value of this technique in establishing the diagnosis at an early age. In some instances surgical intervention may have to be undertaken early, and so early diagnosis becomes imperative.

TABLE 4

BLOOD PRESSURE READINGS IN COARCTATION OF AORTA

Case	Age	Sex	Arm		Leg		Diagnosis Confirmed
1	9 months (pre-op.)	Female	120	130	70	75	By angiocardiography and operation
	13 months (post-op.)		90	90	90	90	
2	3 weeks	Male	62	65	22	25	At necropsy

In these two cases it can be seen that the systolic pressures in the legs are markedly lower than in the arms and that this difference is well outside the range shown for normal infants.

Summary and Conclusions

The flush method is a simple and accurate means for determining the systolic blood pressure in infants. The method is described and is shown to give reproducible results. The gradient of systolic blood pressure between the arms and legs in 27 normal newborn and older infants is recorded. In many the pressure in the legs was lower than that in the arms, but in none was this difference greater than 14 mm. of mercury, and in the majority it was considerably smaller. This contrasts with the findings in adults (Hamilton, Woodbury and Harper, 1936) where the systolic pressure in the femoral artery has been shown to be 20 mm. Hg higher than that in the brachial.

In two infants with coarctation of the aorta of the adult type the systolic pressure in the legs measured by the flush method was 52 mm. and 40 mm. of mercury less than that in the arms.

We are indebted to Dr. Reginald Lightwood and to Dr. Ursula James for the opportunity to study their patients. We would also like to thank Dr. Alexander Nadas of Boston for drawing our attention to the method, and Mr. K. P. Goldman of St. Mary's Hospital Medical School for his assistance.

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CIRCULATING BASOPHILIC LEUCOCYTE COUNTS IN THE NEWBORN

BY

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Recent evidence that histamine is present in basophilic leucocytes (Graham, Wheelwright, Parish, Marks and Lowry, 1952; Code and Mitchell, 1954) as well as in tissue mast cells (Riley and West, 1953) has created fresh interest in these cells. Knowledge of variations in the number of circulating basophils is scanty owing to the inaccuracy of smear techniques, but the introduction of a chamber-counting method (Moore and James, 1953) has made it possible to measure even small changes with considerable accuracy. Using this method, basophils have been counted in the capillary blood of healthy infants during the newborn period.

Method and Procedure

The method used was essentially that described by Moore and James (1953). The intensity of staining with different samples of toluidine blue was found to vary considerably and even the sample which gave the best results (toluidine blue, B.D.H.) had to be used in a higher concentration than that recommended. Moreover, although the counting fluid was found to be satisfactory for older children, haemolysis of red cells in the newborn was incomplete. After numerous trials, satisfactory haemolysis was obtained by reducing the amount of 95% ethyl alcohol to half that recommended. The modified Moore and James counting fluid for use in newborn infants was therefore as follows:

Toluidine blue (B.D.H.) 0·075% in 0·85% saline	40 ml.
95% ethyl alcohol	5·5 ml.
Saturated solution of saponin in 50% ethyl alcohol	1 ml.

With this fluid, the granules in the basophils stain bright pink, while those in the eosinophils are greenish-yellow. The colours are improved if the *p*H of the fluid is carefully adjusted to *p*H 7·75 (James, 1953). Total leucocytes, eosinophils and basophils were counted in the same chamber as described by Moore and James.

The initial counts were made on venous blood from the umbilical cord immediately on delivery; the cord was clamped within a few minutes without waiting for pulsation to cease. All subsequent counts were made on capillary blood obtained by heel stab. A free flow of blood was obtained from the heel without pressure and the first drop was wiped away before filling the pipette. Capillary blood was used for the counts because repeated venepuncture was considered unjustifiable and because the differences between capillary and venous blood have been shown to be small (Lucas, Dearing, Hoobler, Cox, Jones and Smyth, 1921; Findlay, 1946). Moreover, it was felt that counts on capillary blood might have more practical value since blood is more easily obtained from sick infants by heel stab than by venepuncture.

Counts were made at half an hour, four hours, and 24 hours after birth, and thereafter daily to the fifth day, at 1 week and at 6 weeks. All counts from 24 hours onwards were made between 12 noon and 2 p.m. to avoid the possibility of diurnal variation, although this is not known to occur. The counts were made on 20 healthy infants born spontaneously at full term after normal pregnancies. The babies were unselected except in so far as they were born between 11 a.m. and 3 p.m., so that counts on subsequent days would be as nearly as possible at 24-hour intervals.

Results

Table I shows the values obtained for serial basophil counts in each infant. The number of circulating basophils rose after birth to reach a maximum at 24 hours in 17 of the 20 infants, and at four hours in the remaining three. There was a rapid fall between one and three days and a more gradual further decline to the lowest level usually reached on the fifth day. At 1 week the mean count had risen slightly and at 6 weeks was double that recorded at 1 week (Table 2). Although the

TABLE 1
NUMBERS OF BASOPHILS PER C.MM. OF BLOOD

Infant No.	Birth	½ Hour	4 Hours	24 Hours	2 Days	3 Days	4 Days	5 Days	1 Week	6 Weeks
1	23	27	31	22	16	14	11	13	12	14
2	69	84	125	135	68	48	38	24	30	—
3	26	28	33	44	27	28	24	22	24	—
4	20	26	28	38	16	9	14	8	11	25
5	55	72	128	75	44	32	28	13	36	68
6	38	50	83	85	42	26	19	14	16	72
7	22	30	35	41	16	17	16	13	13	22
8	36	38	50	53	25	19	13	17	16	24
9	56	63	69	79	35	26	22	16	13	38
10	18	26	27	31	13	9	9	13	13	47
11	33	38	41	46	19	13	13	9	12	16
12	25	38	41	47	30	—	16	13	17	38
13	30	41	47	61	30	24	21	16	15	31
14	68	61	66	75	56	25	13	11	13	28
15	28	38	44	47	42	26	15	13	13	32
16	20	22	31	39	38	20	22	16	25	28
17	31	41	44	56	32	34	—	24	19	—
18	21	25	28	29	22	12	6	6	7	16
19	6	15	19	13	8	9	8	8	11	15
20	16	16	19	22	13	13	11	13	13	20

basophil counts for the group varied considerably at any one time interval, the changes in each individual were remarkably consistent and adhered closely to the pattern for the mean.

The total leucocyte and eosinophil counts followed the same general pattern (Table 2), but the peak eosinophil count was not reached until the second day, and the eosinophil counts in any one infant showed wide variation.

Comment

Previously recorded data on basophil counts in the newborn have been based on differential counts made from blood smears. Elder and Hutchison (1895) found no basophils in the cord blood of 12 infants. Lippman (1924) stated that basophils are relatively numerous at birth, the average count being 153 per c.mm., and that the number decreases rapidly to 50 per c.mm. at 6 hours and to 6 per c.mm. at 5 days. Kato (1935) reported that basophils are comparatively numerous in the newborn period, but did not give any values. Wegelius (1948) found average counts of 50 basophils per c.mm. at birth and 45 per c.mm. at 2 hours. The present results with the more accurate counting-chamber technique confirm that basophils are numerous in the immediate newborn period, but instead of decreasing the number increases during the first 24 hours, with a rapid decrease thereafter. This decrease after the first day was also reported by Forkner (1929), but the very high values of up to 636 cells per c.mm. found by this author were not found in the present series.

In most of the infants the basophil counts followed the general pattern very closely, in contrast to the eosinophil counts, which fluctuated widely. This does not bear out Lippman's statement (1924) that basophilic leucocytes are the most variable of all blood cells; in fact the basophil counts have been found to be remarkably consistent in any one individual.

The mean values for eosinophil counts and the

TABLE 2

Time interval		Birth	½ hour	4 hours	24 hours	2 days	3 days	4 days	5 days	1 week	6 weeks
Number of counts		20	20	20	20	20	19	19	20	20	17
Basophils per c.mm.	Mean	32	39	49	52	30	21	17	14	16	31
	Range	6-69	15-84	19-128	13-135	8-68	9-48	6-38	6-24	7-36	14-72
	Standard deviation	17·2	18·6	31·0	27·9	30·4	10·2	7·7	4·9	7·1	17·1
Eosinophils per c.mm.	Mean	179	217	234	330	362	312	241	226	266	305
	Range	48-426	68-404	78-438	100-705	153-689	113-582	72-400	60-366	63-460	122-510
	Standard deviation	107	105	116	180	171	142	101	92	104	129
Total leucocytes in thousands per c.mm.	Mean	11·1	14·3	18·3	19·5	12·6	10·4	9·1	9·0	9·6	9·6
	Range	9·1-17·0	10·8-19·0	12·7-26·4	11·2-29·6	8·4-17·8	6·8-15·4	6·3-14·4	6·5-12·5	6·5-13·2	7·7-12·1
	Standard deviation	2·0	1·9	3·7	4·5	2·7	2·3	1·8	1·7	1·6	1·2

changes which occur following birth are very similar to those reported by Lippman (1924). The values are of the same order as those found by Burrell (1953), but the very low counts which she recorded during the first three days and the progressive rise thereafter were not encountered. The total leucocyte counts conform to the general pattern reported by other authors (Lippman, 1924; Forkner, 1929; Kato, 1935; Wegelius, 1948).

In the present state of knowledge concerning the function of the basophil, the significance of the changes which occur in the newborn period is uncertain. There is good evidence that basophils are concerned with the carriage of heparin (Behrens and Taubert, 1952; Martin and Roka, 1953). Furthermore, a relationship between the numbers of basophils and eosinophils and the level of histamine in the blood (Code and Mitchell, 1954) suggests that these two types of cell may share the function of histamine carriage. Little is known about the metabolism of heparin and of histamine in the newborn infant. There is some evidence, however, that the cord blood content of both substances is high (Piccoli, 1950; Pettay, 1950) which would accord with the present observations that both basophils and eosinophils are numerous at birth.

Summary

Circulating basophils have been counted in 20 infants at frequent intervals after birth. The counts were made on capillary blood using a chamber method, and the values obtained have been compared with those reported previously. Counts of eosinophils and total leucocyte counts were made simultaneously.

Basophils are relatively numerous at birth and increase in number during the first 24 hours, decreasing thereafter to reach a minimum level on the fifth day after birth. The number then increases again and at 6 weeks is approximately double that recorded at 1 week.

I am grateful to Professor J. L. Henderson for his advice and criticism.

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THE EVALUATION OF THE EOSINOPENIC RESPONSE TO CORTICOTROPHIN AND CORTISONE IN THE NEWBORN INFANT

BY

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The eosinopenic response to stress has been recognized since Zappert (1893) described its occurrence in certain infections, and in recent years it has been included among the phenomena of the alarm reaction (Selye, 1949).

It was also shown that a decrease in the number of circulating eosinophils followed the injection of corticotrophin or cortisone, and Hills, Forsham and Finch (1948) concluded that stress induced eosinopenia by the release of these hormones.

Thorn, Forsham, Prunty and Hills (1948) demonstrated that the secretion of the adrenal cortex was essential if eosinopenia were to be produced, and from this devised the Thorn test. Following the determination of the absolute eosinophil count an adult receives 25 mg. of corticotrophin and the percentage decrease in four hours is found. Thorn *et al.* believed that a decrement of 50% or more should occur in the presence of healthy adrenal cortex.

The significance of the results is dependent upon the stability of the eosinophil count in normal people over a similar time interval, and it has been shown by Swanson, Bauer and Ropes (1952) from a review of the literature and from a small but carefully studied series of their own that spontaneous variations of this magnitude may in fact occur at certain periods of the 24 hours in adults.

The test has been employed also in newborn infants, but no careful study of hourly changes in the absolute eosinophil level at that age can be found. It was decided, therefore, to undertake an evaluation of the test in the neonatal period by determining the nature of the spontaneous variation over a four-hour interval and to note any relationship that might exist between eosinophil change and disturbance of the baby.

The second part of the investigation was planned to determine what responses could be obtained by the injection of varying doses of corticotrophin and cortisone. Finally it was hoped to determine whether the magnitude of the response varied with the age of the infant.

METHODS

Part I

Three groups of newborn infants, conforming to the criteria of normality previously employed (Farquhar, 1954), were selected at random. The first- and third-day groups each contained 15 infants and there were 16 in the tenth-day group. Six hours were allowed to elapse before studying infants on the first day in order to avoid the rapid eosinophil changes previously described as occurring in that period.

The first count was carried out at 9.30 a.m. in the majority, but at 10.30 a.m. in a few, and thereafter at intervals of one hour until 3.30 p.m.

The infants were fed at 9.45 a.m. and 1.45 p.m. so that all were fed once in the first four hours, or just before starting in a few, and twice in the six hours.

The infant's reaction to the pain of heel-stabbing was also noted and graded as follows: (1) Cried when stabbed and for some time thereafter; (2) cried when stabbed; (3) restless and whimpered when stabbed; (4) no response.

The technique of eosinophil counting was that described by McArthur, Smart, MacLachlan, Terry, Herting, Gautier, Godly, Swallow, Simeone, Zygmuntowicz, Christo, Crepeaux, Point and Benson (1954), and employed in previous work (Farquhar, 1954).

Part II

Varying dosages of corticotrophin and cortisone were injected into different groups of normal newborn infants at 9.30 a.m. and the percentage change induced in the eosinophil count was determined.

The infants in some of the groups were given the same dosage of the hormone on the first, third and tenth days, so providing serial studies of response in individuals. Lest the response to a third injection after the interval of a week might be influenced by the infant's having

received two injections previously, separate groups were given the same dose on days one and three and on days three and ten.

Both the corticotrophin and cortisone were fresh and taken from the same batches. The corticotrophin was later checked favourably against another batch by the same manufacturer and a further batch by another manufacturer. A tuberculin syringe was employed for the injection of cortisone in order to achieve more accurate dosage.

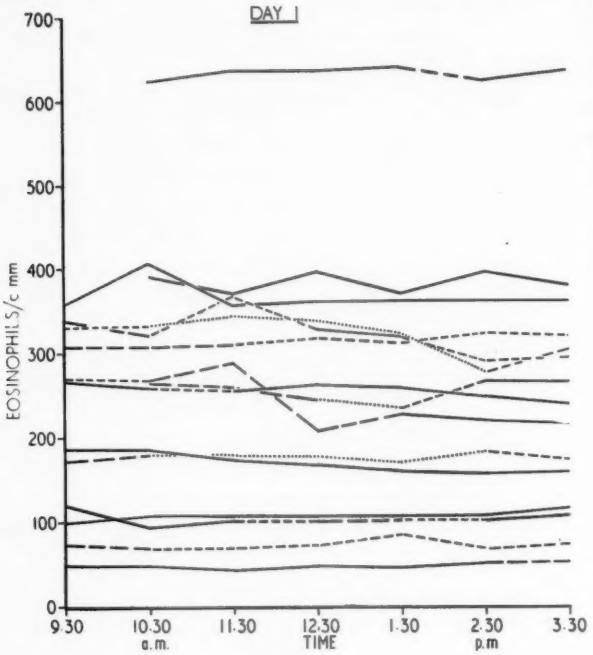

FIG. 1.

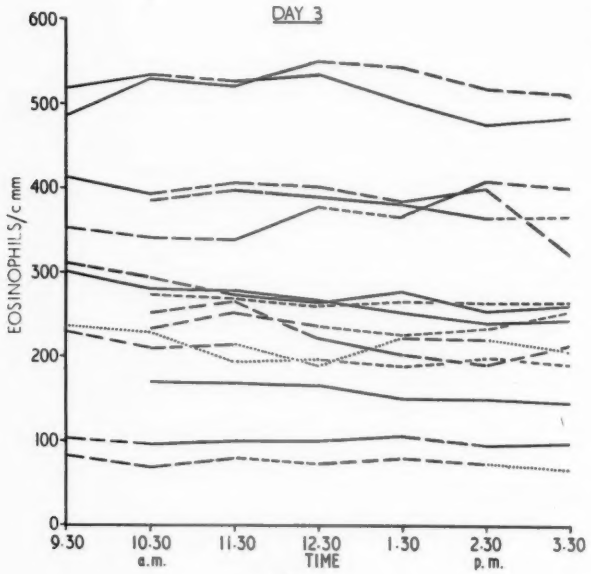

FIG. 2.

RESULTS

Part I

It may be seen (Figs. 1-3) that there was little spontaneous change in the eosinophil counts of individuals during the same six-hour period on the first, third and tenth days of life.

Of the 15 cases studied on the first day there was insignificant hourly variation in 10, a moderate downward trend in three, a slight downward trend in one and the count fluctuated a little in one. Only six of the 15 infants studied on the third day had very stable eosinophil counts. Four showed a slight and two a moderate downward trend, two a slight upward trend and some fluctuation occurred in one. On the tenth day the count was stable in 11 of the 16 infants, two showed a slight and one a moderate downward trend and in two there was a little fluctuation.

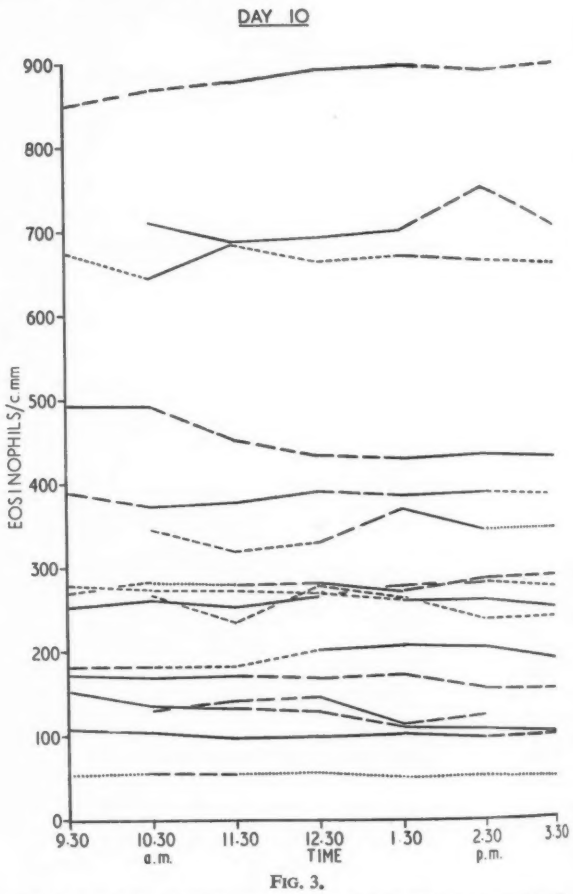

FIG. 3.

FIGS. 1, 2 and 3.—Hourly observations on the eosinophil counts of normal infants on Days 1, 3 and 10.

——————— follows grade I response
— — — — — follows grade II response
- - - - - - - - - follows grade III response
..... follows grade IV response

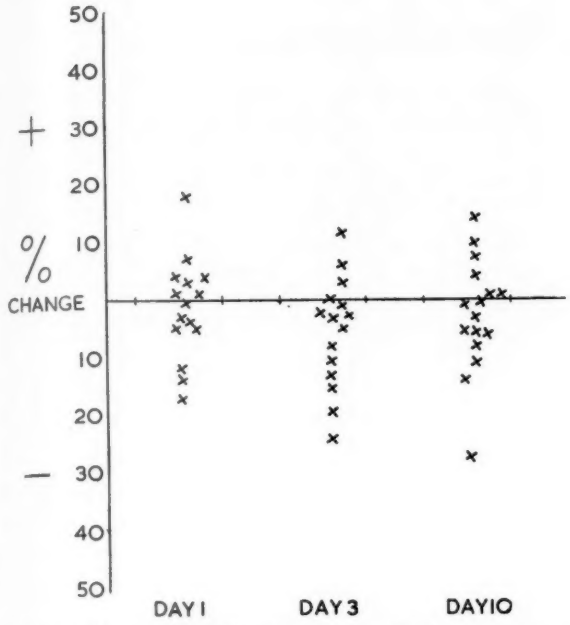

FIG. 4.—Eosinophil levels of newborn infants, showing spontaneous change in four hours on Days 1, 3 and 10 of life.

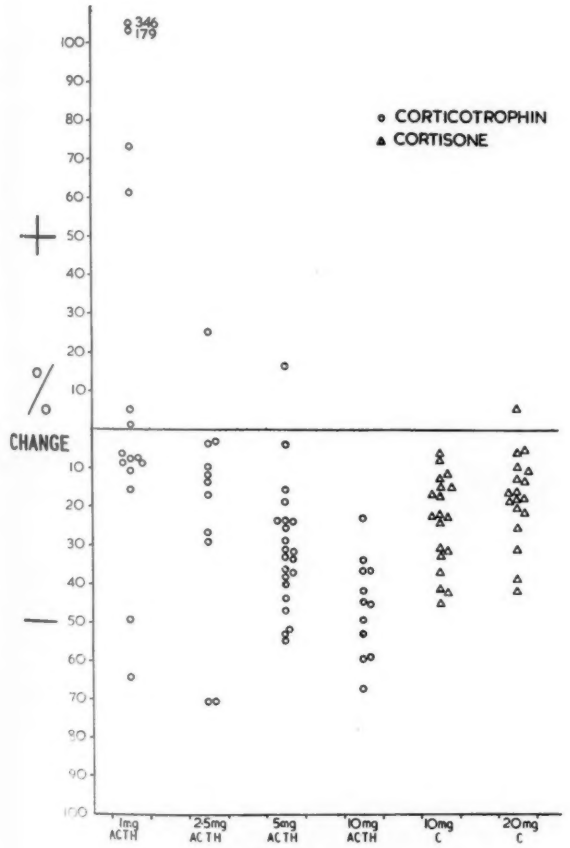

FIG. 5.

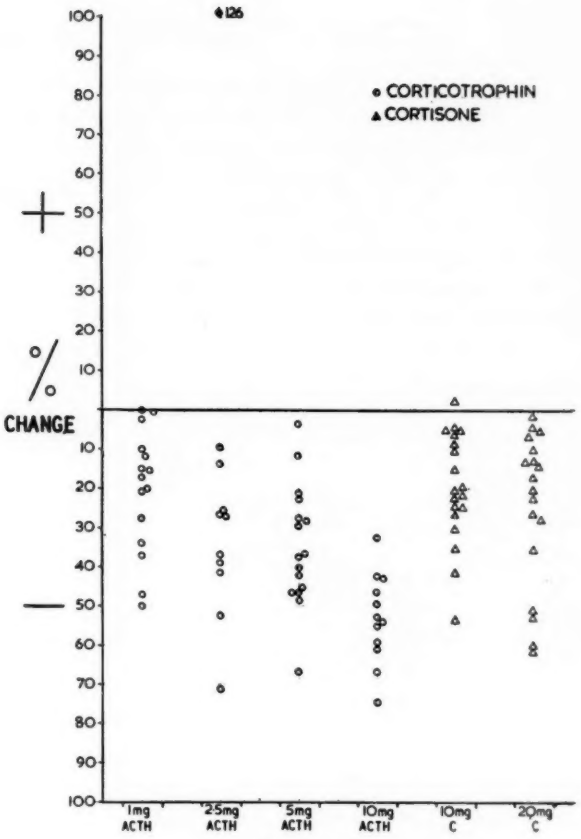

FIG. 6.

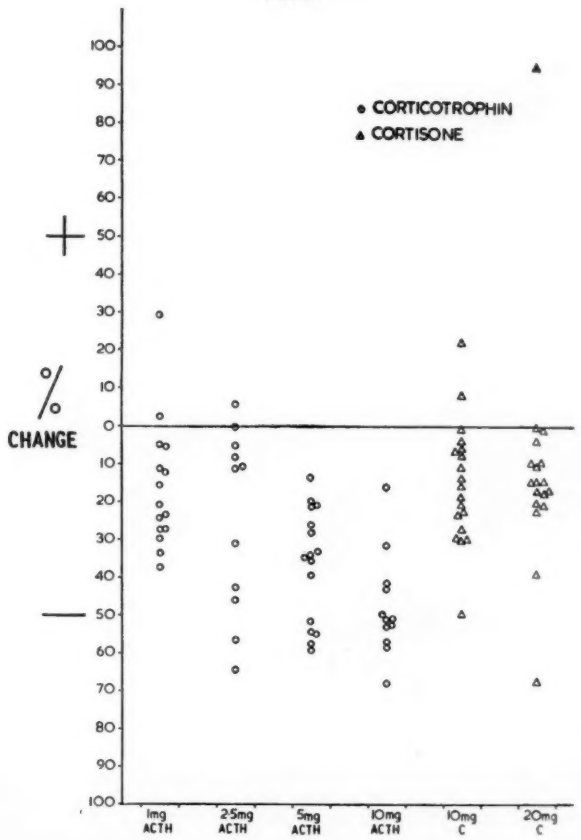

FIG. 7.

FIGS. 5, 6 and 7.—Percentage change in eosinophil counts of normal infants on Days 1, 3 and 10 of life occurring four hours after varying doses of corticotrophin and cortisone.

In 35 of the 46 infants the spontaneous change in four hours was either an increase or a decrease of less than 10%. In only two of the 46 did the decrease exceed 20% (see Fig. 4).

It may also be seen from Figs. 1-3 that there was no correlation between the reaction of the baby to the taking of blood and the change in the eosinophil count over the next hour, nor were the changes related to the time of feeds.

Part II

Induced Change by Corticotrophin. The scatter of changes (expressed as percentages) in the eosinophil counts of the infants studied on the first, third and tenth days of life as the result of injecting 1, 2·5 or 5 mg. of corticotrophin is shown in Figs. 5-7. Two groups were given 10 mg. of corticotrophin, one receiving it on the first and third days and the other on days three and ten, and as the results on day three were almost identical in the two groups, the figures for that day from the first group were used in Figs. 5-7. Similarly, two groups were given 5 mg. corticotrophin in addition to the serial study and again there was little difference between them in the response on the third day.

EOSINOPHILIC RESPONSES. The injection of 1 mg. of corticotrophin resulted in a substantial increase in the number of circulating eosinophils in four of the 15 cases the first day and a small increase occurred in a further two. One of the infants given 1 mg. on the third day also showed an increase in eosinophils.

The injection of 2·5 mg. provoked an increased eosinophil count in different cases on days one, three and ten, whereas only one small increment followed the injection of 5 mg. in a bigger series and none at all after the giving of 10 mg.

EOSINOPENIC RESPONSES. The eosinopenic responses to the different doses of corticotrophin may be seen in Figs. 5-7. The scatter of response to each dose is considerable on each day, but from the graphs and from the frequency distribution table (Table 1), which takes into consideration larger groups of infants, it may be seen that in general the greater the dose of corticotrophin the greater the fall in the eosinophil count.

The mean percentage changes with the varying doses are recorded in Table 2, but when these means are re-calculated after the removal of the large positive values on day one it may be seen from Fig. 8 that the regression lines of the means indicate that a rough arithmetic relationship existed between the degree of change and the dose of corticotrophin injected.

The scatter of response to the varying doses overlaps widely, however, and by comparing Fig. 4 with Figs. 5-7 it may be seen that an appreciable number of the healthy infants studied had a spontaneous eosinolysis in four hours as great as that which in some followed the injection of corticotrophin. Certainly, with doses of 2·5 mg. or less, so many of the eosinopenic responses lay within −20% that such a result would have no significance in individual cases. With 5 mg. a minority of

TABLE 1

FREQUENCY DISTRIBUTION OF EOSINOPHIL RESPONSES

Stimulus	Dose (mg.)	Day	Positive	Negative Response (%)					No. of Infants Studied
				0–9	10–19	20–34	35–49	>50	
Nil	—	1 3 10	7 3 4	5 7 9	3 3 2	2 1			15 15 16
Corticotrophin ..	1	1 3 10	6 2	5 3 2	2 5 3	4 7	1 2 1	1 1	15 15 15
	2·5	1 3 10	1 1 1	2 3	4 2 2	2 3 1	3 2	2 2 2	11 11 11
	5	1 3 10	1 1	1 3 1	2 4 1	11 16 16	6 16 10	3 9 11	24 48 40
	10	1 3 10			1 1	2 2 1	6 6 2	4 15 8	12 24 12
Cortisone	10	1 3 10	1 2	4 6 9	6 12 8	7 21 21	7 7 2	1 1	24 48 43
	20	1 3 10	1 1 1	3 8 4	8 12 7	4 8 4	2 2 1	5 1	18 36 18

the responses was less than −20%, but only with 10 mg. was there almost universal response beyond that figure.

From the groups studied no significant evidence can be found to indicate that the response to corticotrophin was any more or less efficient on any of the three days.

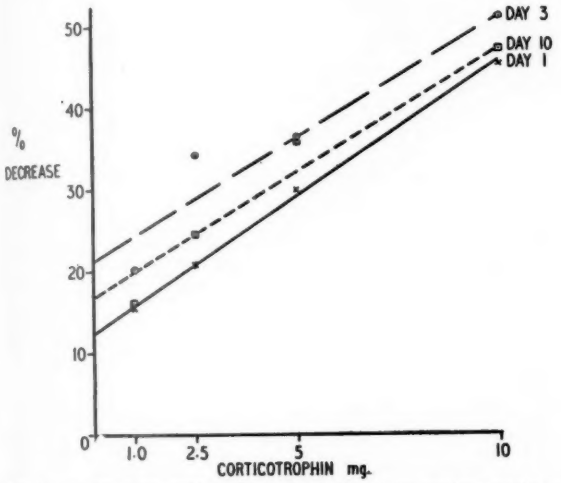

FIG. 8.—Average percentage decreases induced by corticotrophin in normal infants on Days 1, 3 and 10.

Induced Changes by Cortisone. The results of injecting cortisone may be seen also in Figs. 5-7 and in Tables 1 and 2.

Only one significant eosinophilic response was obtained, and unlike those from corticotrophin it occurred on the tenth day.

As with corticotrophin there was considerable individual variation in eosinopenic response, and over the four-hour interval the response of the cortisone group as a whole was appreciably less than the response of the groups receiving half the dosage (by weight) of corticotrophin.

It may be seen also that the responses of the group receiving 20 mg. of cortisone were on the whole smaller than those of the group receiving 10 mg. The mean change on the third day with the greater dosage is in fact larger, but this is due to the influence on the mean of four decrements which fall well below the main scatter of responses.

DISCUSSION AND INFERENCES

Spontaneous variations sufficiently great to invalidate the Thorn test were described by Rud (1947) in adults, but he used an acetone stain which has been recognized as being capable of introducing error into eosinophil counting.

Swanson *et al.* (1952) undertook a careful study of the hourly spontaneous changes in adult absolute eosinophil values, and substantiated that diurnal variation did occur and that it was sufficiently great in the mornings to invalidate the test if carried out then. They concluded, however, that the eosinophil count was sufficiently stable in the afternoons to justify Thorn testing even although spontaneous decrements of up to 40% were found. It was postulated that the stress of wakening and the relaxation of sleep might exert an important effect on the number of circulating eosinophils and would explain why the spontaneous changes are commoner and greater in the morning. Tatai and Ogawa (1951) studied normal sedentary adults and found that the

TABLE 2
MEANS OF EOSINOPHIL CHANGES

Stimulus		% Change in Four Hours			No. of Infants in Group
		Day 1	Day 3	Day 10	
Nil (i.e. 'spontaneous change')		− 1·5	− 5·7	− 2·5	15
Corticotrophin					
mg. 1	Serial study	+32·6	−20·6	−16·0	15
mg. 2·5	Serial study	−20·8	−19·7	−24·5	11
mg. 5	Serial study	−30·0	−34·6	−36·5	16
	Comparative groups . .	−30·1	−34·5 −38·5	−36·0	24 24
mg. 10	Comparative groups . .	−45·7	−53·0 −49·9	−47·6	12 12
Cortisone					
mg. 10	Serial study	−23·6	−19·5	−14·9	19
	Comparative groups . .	−24·4	−21·5 −22·7	−20·9	24 24
mg. 20	Comparative groups . .	−17·4	−24·7 −24·5	−11·7	18 18

absolute eosinophil count was maximum at night during sleep and minimum in the waking daylight hours.

Following the adjustments made by the infant to the start of extra-uterine life he is subjected to fewer stresses than the adult and his day is not divided into the same compartments of stress and relaxation. Much of his 24 hours is spent asleep protected from sudden changes in environmental temperature and with the sole disturbance of regular feeding. It was important, therefore, to determine whether the diurnal variation obtaining in adults occurred in newborn infants and whether feeding, with the associated processes of weighing and changing, or the painful stimulus occasioned by the taking of blood, were able to induce eosinophil decrements greater than 50%.

Leucocyte counts at 15-minute intervals over three or four hours following bottle feeds were carried out by Mitchell (1915), and variations in the number of white cells were found. No particular attention was paid to eosinophils and there was no proof that the process of digestion was really responsible for the fluctuations. Washburn (1934) performed serial total white cell and differential counts on infants over the interval 9 a.m. to 5 p.m. and failed to find any pronounced variation in the total number of leucocytes. Those which did occur were produced largely by lymphocytic changes and were not related to ingestion, digestion, sleep, increased activity, or minor external disturbance. No absolute figures for eosinophils were given in the paper but the line of the hourly eosinophil values is depicted on the graphs of several infants, and, although they appear fairly stable, they are close to the base-line and the small fluctuations which do appear may amount to decrements of 30% or more.

In the present groups studied on the first, third and tenth days of life considerable stability of the eosinophil count over the same six hours in individual infants was found. Particular attention was paid to such spontaneous changes as might occur in the time interval zero to four hours for comparison with the eosinopenic responses to corticotrophin and cortisone. Usually at four hours the eosinophil count fell within the range $\pm 10\%$ of the original value; in only two of the 46 individuals (4%) were the decrements in excess of 20% and in neither did they amount to 30%.

Farquhar (1954), in a personal series and from a review of the literature, observed a trend toward higher eosinophil values on the third day than at any other time in the first 10 days with the exception of birth. The evidence suggesting under-activity of the adrenal cortex following upon the immediate response to the stress of birth was reviewed, but no correlation between day-to-day eosinophil and blood glucose change was found to substantiate the suggestion (Farquhar, 1954; Talbot, Sobel, McArthur and Crawford, 1952) that the explanation of the group trend toward rising eosinophil counts and falling blood glucose levels in the first few days might be that the production of 11-17 oxycorticosteroids was depressed at that time.

White and Sutton (1950) observed the eosinopenic responses of infants to adrenaline, accepted decrements of 35% or greater as implying normal adrenocortical response and regarded anything less than a 30% decrease as abnormal. Employing these criteria they concluded that the pituitary-adrenal response in healthy, full-term infants was normal, but no attention was paid to the age of the subject in days. Since the publication of their paper, however, the use of adrenaline in the test has fallen into disrepute in view of such inconsistent results as those demonstrated by Kark and Muehrcke (1952) among others.

The Thorn test employing corticotrophin has been shown to be of value in the assessment of the efficiency of the pituitary-adrenal mechanism in adults, provided it is remembered that 'it is subject to the limitations common to most laboratory tests' (de Mowbray and Bishop, 1953), and provided that the test is carried out in the afternoon to avoid the greater spontaneous variations occurring in the morning.

Klein and Hanson (1950) employed corticotrophin in the Thorn test on older children and seldom induced decrements much greater than 37%. Employing this as their standard of normality they carried out the test on newborn infants. The infants of one group were tested once in the first three days and again in the second week with much better and more consistent falls in the latter. Two other groups were studied, one in the first week and the other in the second, with similar results. With 1 mg. or less of corticotrophin fewer 'positive' Thorn tests were obtained than when the dose was increased to 2-12 mg. and the 1 mg. dose was considered to be the more sensitive in demonstrating adrenocortical hypofunction. Venning (1950), however, employed much larger doses of corticotrophin in a small series and induced greater eosinophil responses in the second than in the first week.

In the present study doses of 2·5 mg. or less of corticotrophin were inadequate to provoke eosinopenic responses beyond the range of spontaneous change and appeared in some cases to induce an eosinophilia. The injection of 5 mg. was followed by an eosinopenia beyond the spontaneous range in

the majority of cases, but only with 10 mg. was such a response consistently obtained.

In the groups studied, therefore, the dose of corticotrophin required to provoke eosinopenic responses greater than 20% in newborn infants was two-fifths as great as that required to induce a decrease of over 50% in the normal adult although the body weight of the infant was only about one-twentieth of the adult weight. Furthermore, even with this relatively high dose of corticotrophin decrements of 50% or greater occurred in about half the subjects only. The magnitude of the response was roughly proportionate to the dose given, but the dosages were so high relative to body weight that impotence of the particular batch of corticotrophin might be suspected had it not been excluded by comparison with others. These observations provide further suggestive evidence that relative inefficiency of the adrenocortical response to corticotrophin exists at this age.

White and Sutton (1950) found that adrenaline was relatively ineffective in provoking eosinopenia in premature infants, and, in order to exclude the possibility that this might be due not to functional under-activity of the adrenal but to abnormal resistance of the eosinophils to cortisone, they injected six infants with whole adrenal cortical extract and obtained an adequate eosinopenic response in all. They concluded that there was inability on the part of the premature infant to elaborate sufficient amounts of adrenal cortical hormone in response to corticotrophin. Klein and Hanson (1950) injected whole adrenal extract into 11 infants in the first two days of life with a view to excluding eosinophil resistance and obtained eosinopenic responses greater than 37% in eight of them in four hours.

In the present study cortisone was employed in preference to lipo-adrenal extract and proved to be less effective in inducing eosinopenia than half the dose by weight of corticotrophin. This at first appears to suggest eosinophil resistance. Evidence in favour of the suppression of adreno-cortical function by cortisone was published by McIntosh and Holmes (1951), and the more likely explanation of the poorer response to 20 mg. is that the injection of cortisone depressed endogenous adreno-cortical function and the resulting total of available cortisone was less than would have followed a smaller dose of corticotrophin.

The absolute eosinophil levels in Part I of this investigation were rather higher on the tenth than on the third day and so differed from the figures already published (Farquhar, 1954) and the figures from which the eosinopenic responses were calculated in Part II of this study, both of which series were larger and showed higher absolute values on the third day. It had been considered possible that applying the Thorn test to newborn infants on the third day would show that the eosinopenic responses indicated a relative degree of adrenal cortical hypofunction compared with those induced on the first and tenth. The comparison of the group responses to corticotrophin on the three days, however, shows no significant difference between them, and if there is any doubtful trend at all it is toward rather better responses on the third day.

The Thorn test is of little value in the assessment of the health of the pituitary-adrenal axis in newborn infants because, unlike in adults where the great diurnal variation is the handicap, the response to relatively great doses of corticotrophin is so poor that it may be within the range of spontaneous variation.

In these conditions it is almost impossible to define what the normal eosinopenic response of a normal newborn infant to corticotrophin should be, but from the experience of this study it appears that the criteria might be a decrement of 30% or greater when 10 mg. are injected.

SUMMARY AND CONCLUSIONS

The literature referring to the Thorn test in adults and newborn infants is briefly reviewed.

The evaluation of the test in the newborn infant depends upon (*a*) the range of spontaneous eosinophil change, and (*b*) the range of eosinopenic response to varying doses of corticotrophin.

Serial hourly studies of eosinophils in healthy infants showed considerable stability of absolute levels, and such fluctuations as did occur were unrelated to feeding and minor upsets.

Increasing doses of corticotrophin induced a proportionate increase in the mean eosinopenic response. There was, however, a considerable range of response to each dose on each day, and 10 mg. of corticotrophin were required to induce decrements greater than 30% consistently.

There was no significant difference in the nature of the response to the varying doses on the first, third and tenth days of life.

The Thorn test at this age is of little value because the poor eosinopenic responses to corticotrophin may fall within the range of spontaneous change. A normal response might be defined as a decrement of 30% or greater when a 10-mg. dose is injected.

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Dr. E. C. Fahmy for permission to carry out these investigations in his obstetric unit, to Professor R. J. Kellar for laboratory space, to Professor D. M. Dunlop for supplies of corticotrophin and cortisone, and to Sister E. S. Somerville for invaluable help. Finally, I should like to pay tribute to Miss Pat Steven for her meticulous technical work in the laboratory.

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THE EFFECT OF DISEASE AND INJURY ON THE ADRENAL CORTEX OF STILLBORN AND NEWBORN INFANTS

BY

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The activity of the adrenal cortex in the newborn has usually been studied biochemically or by the response to stimuli which are adequate in the adult (Bongiovanni, 1951; Heller, 1954). Such investigations have been made on normal, healthy infants. The effect of systemic disease on the adrenal cortex of children, from birth to 15 years, has been studied morphologically by Stoner, Whiteley and Emery (1953). Changes in the adrenal cortex of the foetus and newborn infant may be (*a*) specific, i.e., peculiar to the disease or injury suffered by the infant, such as the occurrence of haemopoietic foci in the adrenals in haemolytic disease, or (*b*) non-specific, i.e., not peculiar to the disease or injury suffered by the infant. The non-specific response is usually recognized by variations in the lipid content of the adult (definitive) zone of the cortex.

This paper records an investigation into the non-specific response to disease and injury of the definitive zone of the adrenal cortex in stillborn foetuses and infants dying during the first week of life.

Material and Methods

The material for the study of the non-specific response of the adrenal cortex consisted of a sample of 158 cases drawn from a pool of about 1,900 necropsies performed on stillborn foetuses and newborn infants. The sample was unselected except that macerated foetuses were excluded and none surviving seven days or more was included. The sections of the glands were stained routinely by haematoxylin and eosin and, for lipid, by Sudan IV and haemalum.

Assessment of Changes in Lipid Content of Adult Cortex. Although in adrenals of this age the definitive cortex cannot be divided into the three classical zones, yet there is an ill-defined architectural difference between the sub-capsular region and that adjacent to the foetal cortex. This difference is reflected in the lipid content of the definitive cortex, the outer (sub-capsular) third usually containing less lipid than the inner two-thirds during the first week of life. In the first place the lipid content of the two parts was assessed separately. It was then found that the changes in the outer third ran closely parallel to the changes in the inner two-thirds and thus the state of the definitive cortex could be assessed as a whole.

For the sake of brevity and clarity, and without prejudice to any other meaning, the following terminology was adopted. The cortex was considered to be 'resting' if it contained abundant sudanophilic droplets (Fig. 1),

FIG. 1.—Resting adrenal cortex. The definitive cortex is packed with lipid. From a full-term female infant, aged 1 day, dying from congenital morbus cordis. Sudan IV and haemalum; × 90.

which in the inner two-thirds were large; to be 'active' when the number and size of the droplets had diminished (Fig. 2); and 'exhausted' when there was complete loss of sudanophilia in the definitive cortex. When the diminution in sudanophilia was slight it was frequently patchy.

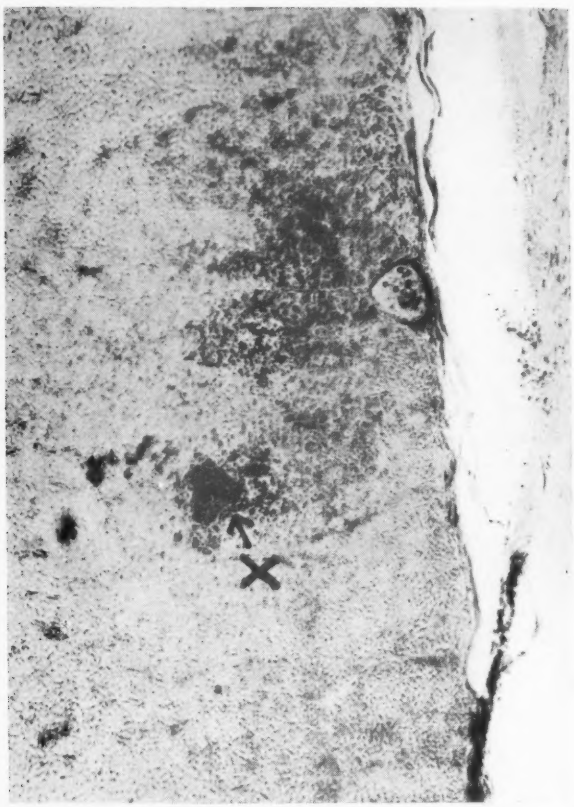

FIG. 2.—Active adrenal cortex. In the definitive cortex there is a general diminution of sudanophilia, more obvious in the subcapsular zone. The distribution is patchy. A haemopoietic focus can be seen (X). From a full-term male infant, aged 36 hours, dying from haemolytic disease. Sudan IV and haemalum; × 90.

Results

Variation in Sudanophilia with Age. The changes in lipid content of the adult cortex with age are shown in Fig. 3. The proportion of stillborn infants with resting adrenals was just under half (28 out of 64) and diminished to a minimum in those dying between 12 and 24 hours, after which it rose to about the level in the stillborn group. This fall in the frequency of resting glands was not statistically significant, as tested by a 2 × 2 contingency table, but it suggested that further analysis might be interesting.

In this figure and in those that follow the area of each circle represents the number of cases in the corresponding sub-group and the areas of the sectors the number of cases in which the adrenals are resting, active or exhausted, respectively. Apart from Fig. 3, the active and exhausted adrenals are grouped together as 'diminished' sudanophilia.

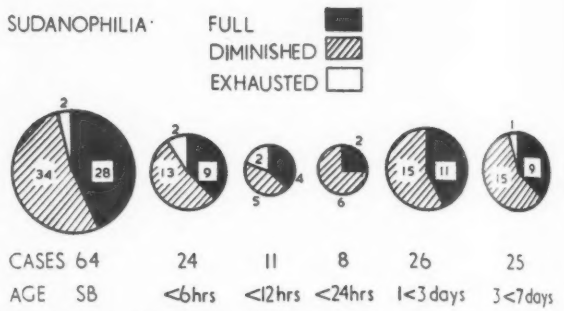

FIG. 3.—The relation between the sudanophilia of the definitive cortex and the age at death in 158 infants.

Asphyxia. The upper part of Fig. 4 shows that among asphyxiated infants there was no change in frequency of resting glands in infants who survived compared with those who were stillborn. The term 'pure' asphyxia is used to indicate that in these infants neither injury, infection nor other disease was found at the post-mortem examination. In none of these 33 cases was there evidence of focal necrosis or arteriolar changes in the adrenal.

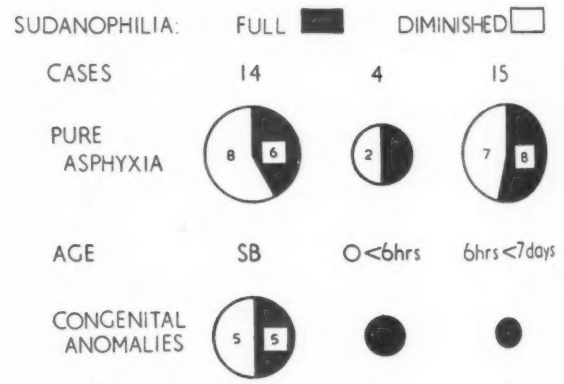

FIG. 4.—The effect of 'pure' asphyxia and congenital anomalies on the lipid content (sudanophilia) of the definitive cortex.

Congenital Anomaly. The lower part of Fig. 4 shows that in stillborn infants the frequency of resting glands was not significantly different in those dying of congenital anomalies from that in those dying of asphyxia and of injury; there was no evidence that survival reduced this frequency. This group of congenital anomalies was small because of the exclusion of those dying with any other detectable lesion.

Birth Injury. The effect of birth injury was examined both in respect of cases of 'pure' birth injury, i.e., infants dying with no complication, and also those in whom the injury was combined with asphyxia. These two groups gave essentially the same result; because of this and because asphyxia, by itself, had no effect on the incidence of resting glands, the results have been combined in Fig. 5.

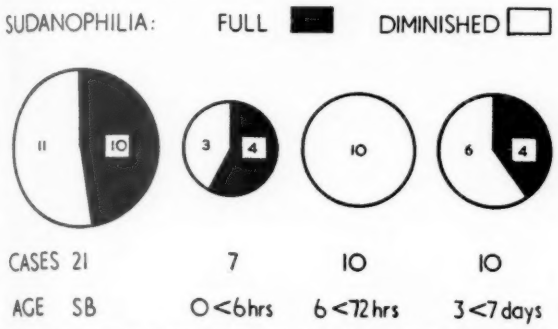

FIG. 5.—The effect of birth injury on the lipid content (sudanophilia) of the definitive cortex.

Both in stillborn infants and in infants dying within six hours of birth the frequency of resting adrenals was essentially the same as in the groups of 'pure' asphyxia and congenital anomalies. None of the infants dying between six and 72 hours after birth had resting glands, all showed diminution of adrenal cortical sudanophilia and two were exhausted. These differences are statistically significant (see Table 1). After three days four of 10 infants had resting glands.

TABLE 1
THE EFFECT OF BIRTH INJURY

State of Definitive Cortex	Stillborn or Surviving Less than 6 Hours	Dying between 6 and 72 Hours	Total
Resting	14	0	14
Active or exhausted ..	14	10	24
Total	28	10	38

Whence P is less than 0·005. This indicates that when infants die from birth injury active or exhausted glands are significantly more common in infants dying between six and 72 hours than in stillborn infants and those surviving less than six hours.

It should be emphasized that this was an unselected sample drawn from a much larger population. Another sample would be expected to have the same general pattern but to differ in detail. For example, infants are occasionally found dying between six and 72 hours after birth in whom the definitive adrenal cortex is in the resting condition, but such cases are infrequent and do not invalidate these findings.

Haemolytic Disease. Eighteen infants out of the sample of 158 suffered from haemolytic disease (Fig. 6). Of those who were stillborn or died

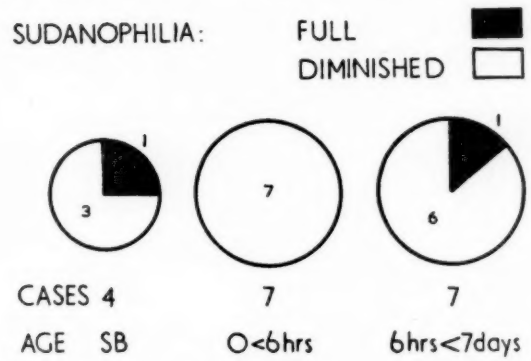

FIG. 6.—The effect of haemolytic disease on the lipid content (sudanophilia) of the definitive cortex.

within six hours, only one out of 11 had adrenals in a resting state. Compared with the effects of asphyxia, congenital anomaly and birth injury this is statistically significant (Table 2). Likewise there was a marked difference between those dying of haemolytic disease between six hours and seven days and those dying of asphyxia and congenital anomaly.

TABLE 2
COMPARISON OF HAEMOLYTIC DISEASE WITH OTHER CAUSES OF DEATH IN STILLBORN INFANTS AND INFANTS SURVIVING LESS THAN SIX HOURS

State of Adult Cortex	Other Causes	Haemolytic Disease	Total
Resting	29	1	30
Active or exhausted ..	29	10	39
Total	58	11	69

Whence P is 0·0113. This indicates that when infants die from haemolytic disease active or exhausted glands are significantly more common than in infants dying from other causes at this age.

Pneumonia. Pneumonia was present in 11 infants and was usually associated with a complicating lesion such as asphyxia or birth injury. This group is too small for a detailed analysis. Of the five infants who were stillborn or who died within six hours of birth, three showed some loss of sudanophilia in the definitive cortex and one complete loss. This pattern is similar to that found in haemolytic disease. Of those who survived more than six hours, only three out of six showed diminution of sudanophilia.

Weight of the Adrenal in Relation to Lipid Content. Selye (1936a, 1936b) showed that in the mature rat the adrenal responds to noxious stimuli in the phase of the 'alarm' reaction by loss of lipid and increase in weight. In Fig. 7 the straight line is the regression line of adrenal weight on body weight for those infants in whom the adrenals were in the resting state. The curved, interrupted lines indicate the limits within which 95% of the resting adrenals lie. When the weights of the adrenals showing diminution in lipid are superimposed on this framework there is no evidence of increase in weight with loss of lipid from the adult cortex; most of the points lying within the 95% range and being symmetrically distributed about the regression line. Cases of haemolytic disease have been excluded from this analysis because the adrenal is affected by changes specific to that disease such as oedema (Burne and Langley, 1955).

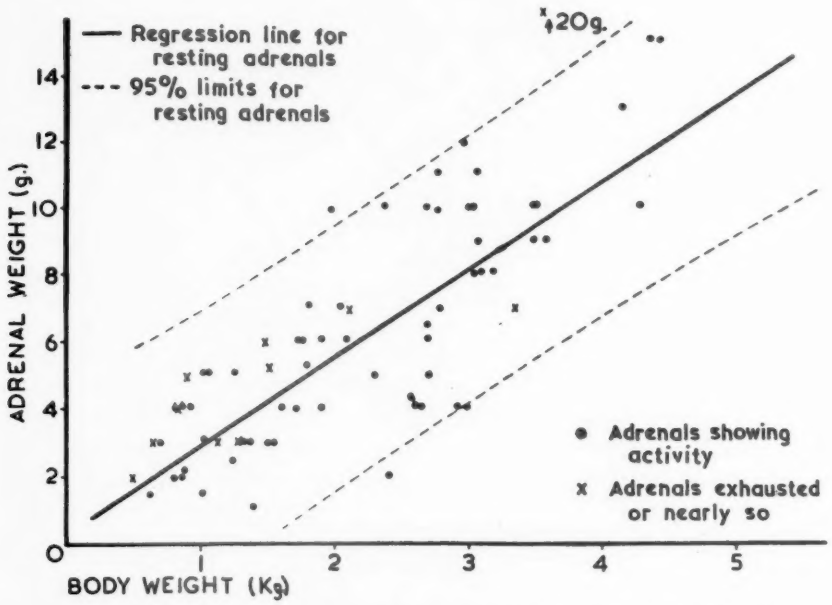

FIG. 7.—The relation between adrenal weight (both glands together) and body weight.

Prematurity. In the preceding analysis no consideration has been given to the effects of prematurity, full-term and premature infants being grouped together. The adult cortex of live-born infants showed less sudanophilia in premature than in full-term infants (Fig. 8). This difference (which is not statistically significant) might be attributed to lack of development of sudanophilic granules in premature adrenals. This was not so, since in stillborn infants full sudanophilia was as frequent in the adrenals of premature infants as in those born at full term.

Discussion

Infants who suffered birth injury showed diminution of lipid in the definitive cortex six to 72 hours after birth; the loss of lipid occurred less frequently in those who survived more than three days. Two interpretations of this are possible. First, that between six and 72 hours the adrenal response to injury reaches a maximum to be followed by a recovery phase, or secondly, that adrenal failure plays a part in causing death in the first three days of life. Since this is not an animal experiment there is no way of deciding between these two possibilities. The pattern is clearly similar to that in adult rats exposed to noxious agents (Selye, 1936a; 1936b) in which, after a latent period of six hours, an 'alarm' reaction occurs which lasts up to 48 hours and is characterized by loss of adrenal cortical lipid and by adrenal hypertrophy. Adrenal hypertrophy was not detected in this series (see Fig. 7) either because it did not occur or because of the relatively large size of the foetal zone masking changes in the adult zone.

Haemolytic disease of the foetus and newborn, in contrast to birth injury, is a chronic disease which starts to affect the infant before birth and the response of the adrenal differs. Both in the stillborn group and in infants who survived up to six days there was, as a group, diminished cortical lipid. This corresponds to Selye's third stage of the stress syndrome which occurs when the noxious stimulus is slight and prolonged. Stoner *et al.* (1953) found little response to haemolytic disease, five out of six cases in their series being in the resting phase. The adrenal response to pneumonia in stillborn infants and in infants surviving less than six hours was similar to that in haemolytic disease. Perhaps this is because infection may precede delivery by some hours, e.g., when the membranes have been ruptured 48 hours, or owing to the cumulative effects of the multiple lesions which are usually present.

Although the adrenal response of neonatal infants resembles the stress reaction described by Selye in adult rats there are a number of differences. The response to stress in rats affects the fasciculate zone (Greep and Deane, 1949). In the alarm reaction this zone suffers lipid depletion and enlargement. In the newborn infant there is no recognizable zona fasciculata; the lipid depletion affects the whole width of the definitive cortex and no enlargement can be recognized by increase of weight or thickness. In the adrenals of rats an increase in sudanophilia occurs in the 'resistance' phase with a marked increase in birefringence, which is maintained after the secondary fall in sudanophilia begins. This present study of neonatal adrenals is based on material obtained at routine post-mortem examinations over a period of years and no refined histochemical tests have been used. Thus it has not been possible to distinguish between a resting gland and one in the resistance phase, and glands showing full sudanophilia in infants dying from four to six days after birth may be in the phase of 'resistance'. Since the functional roles of the zones in the human adrenal are not necessarily the same as in the rats (Bergner and Deane, 1948), and since we are considering the response of an immature adrenal, the comparison between the adult rat and the infant must not be pressed too far.

The infant adrenal appears to show no response to asphyxia in terms of changes in sudanophilia of the definitive cortex. Gruenwald (1951) described other changes in the adrenal, namely, focal necrosis and haemorrhage. We have seen such necrosis of the adrenals but not in this series and not associated with uncomplicated asphyxia. Thus two cases were of haemolytic disease dying at 20 min. and four days respectively, and another in which there was a clinical history of asphyxia in a stillborn infant, but no evidence of such at necropsy. It may well be that necrosis is a response to chronic stress, as described by Selye and Stone (1950), rather than to asphyxia. Haemorrhage occurs in many parts of the body in asphyxia and there is nothing especially odd in its occurring in the adrenal. It is probable that the foetus is adapted metabolically to anoxia, by use of anaerobic mechanisms (Wilson, Reardon and Murayama, 1948), and thus asphyxia is not an adequate stimulus to set going the stress reaction.

Wolman (1952) showed that the eosinophil response to A.C.T.H. was the same in premature as in full-term infants. Jailer, Wong and Engle (1951) tested adrenal function by the effect of injected adrenalin on the eosinophil count and found that there was less fall in the count the more premature the infant. Since response of the adrenal cortex to adrenalin is mediated through the pituitary, whilst that to A.C.T.H. is a direct response of the adrenal it may be supposed that the observations of Jailer *et al.* reveals immaturity of the pituitary-adrenal axis in premature infants. If the reaction of the adrenal to birth injury and haemolytic disease is a stress reaction in Selye's sense then it is mediated by the pituitary-adrenal axis. Using the yardstick of diminished cortical lipid we have failed to demonstrate immaturity of this mechanism.

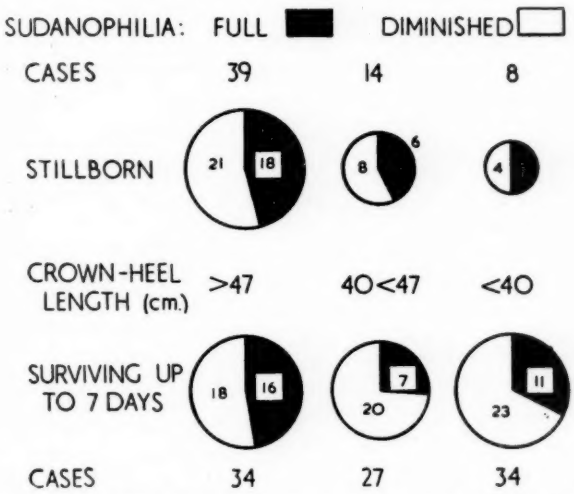

FIG. 8.—The effect of prematurity on the lipid content (sudanophilia) of the definitive cortex.

The results of Stoner *et al.* (1953) differ from ours in a number of ways, probably because their method of assessment of the morphological changes is different. They write, 'At birth the [lipid] droplets are fairly uniformly distributed between the surface and the junction of the adult [definitive] cortex with the X-zone. A few days after birth they tend to become concentrated in the inner half of the adult cortex', and quote Sarason (1943) in support of this description. In our observations this appearance is well recognized, but is associated with a general fall in sudanophilia and is considered to represent adrenal activity; Stoner *et al.* finding it in their control series consider it 'normal'. Their controls are described as instances of sudden death, 'stillbirth, asphyxia, road accident, etc.'. It seems unlikely that more than a few of their 23 control infants died in the first week as a result of road accidents or that stillbirth or asphyxia can be considered normal. We have taken the view that no infants dying under seven days can be used as normal controls; the changes in adrenal morphology can best be assessed by comparing groups of infants in

relation to the disease or injury causing death and the duration of survival.

Summary

The definitive adrenal cortex of stillborn and newborn infants showed no response to asphyxia. Birth injury caused a diminution of cortical lipid six to 72 hours after birth; the diminution occurred less frequently in those who survived more than three days. Haemolytic disease, in contrast to birth injury, is a chronic disease starting before birth, and the response differed; both in the stillborn group and in infants who survived up to six days there was diminished cortical lipid. Neonatal pneumonia, beginning before birth, also caused a reduction in cortical lipid.

It is concluded that the definitive adrenal cortex at birth is responsive to disease and injury. The relationship of this to Selye's stress syndrome is discussed.

We should like to thank Professor A. C. P. Campbell for reviewing the manuscript and Mr. P. Stuart for the photomicrographs and assistance with the charts.

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A CASE OF GALACTOSAEMIA WITH SPECIAL REFERENCE TO MENTAL DEVELOPMENT

BY

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Galactosaemia was originally described by von Reuss in 1908 and since then a number of cases have been reported. From a study of these a fairly characteristic picture is presented, the most constant features being failure to thrive, hepatomegaly, galactosuria and albuminuria. Other less constant features are mental retardation, jaundice, vomiting, cataract, pyrexia, diarrhoea and a tendency to bleed.

From a description of reported cases the disease appears to vary considerably in its severity. Some patients die in early infancy and, judging from retrospective studies, perhaps some die undiagnosed. Other cases appear to be less severe and may not be diagnosed for several months. One patient reported by Donnell and Lann (1951) was not diagnosed for 13 months though he had had 'nutramigen' for a period. Bray, Isaac and Watkins (1952) report a case diagnosed at 7 years.

With treatment by excluding lactose from the diet many of the clinical features, such as galactosuria and hepatomegaly, disappear and the patients show rapid improvement in physical development. Fox, Fyfe and Mollison (1954) suggest that if therapy is begun early the manifestations of the disease may be reversible, but if delayed, prognosis is poor.

The purpose of this paper is to record the clinical picture and development of a severe case diagnosed in early infancy and kept on a lactose-free diet except for the first month, at which time the diagnosis was presumed, and a period of 14 days when the child was transferred to University College Hospital under Dr. C. E. Dent for confirmation of the diagnosis and for reassessment of his tolerance to galactose. During this latter period the mechanism of amino-aciduria was investigated, and the results of this investigation are presented by Cusworth, Dent and Flynn in the following paper.

Case Report

M.McK., a boy aged 3 years, was born at full term in September, 1951, weighing 7 lb. 1 oz. His mother was physically healthy. The reputed father was stated by the mother to be healthy but he was not interviewed personally by us. The mother had two siblings alive and well and one of her sisters died of heart disease at 17 years. The mother's parents were alive and well at the time of the infant's birth.

The baby appeared well until 7 days old when it was noted that he was not gaining weight and was reluctant with feeds. At 9 days old he was becoming increasingly lethargic and developed jaundice. A small quantity of blood was passed in the stools. The liver and spleen were enlarged and the baby's weight had fallen to 5 lb. 12 oz. At this stage septicaemia was suspected and the child was placed on chemotherapy. At 10 days old the baby began to vomit and this persisted until he was admitted to Queen Elizabeth Hospital at 12 days of age.

He was extremely ill, lethargic, and deeply jaundiced. He had a bilateral conjunctivitis and the umbilicus was a little moist. The heart and lungs were normal and there was no obvious abnormality of the central nervous system. The liver was enlarged three fingerbreadths below the right costal margin and the spleen was palpable 1 inch below the left costal margin.

Blood culture was negative. Swabs from the eyes, throat and umbilicus grew *Bact. coli*. The serum bilirubin level was 26 mg. per 100 ml., alkaline phosphatase 29 units, thymol turbidity 4 units. The urine showed a cloud of albumin on boiling and there was a complete reduction of Benedict's reagent. No excess of amino-acids in the urine was reported. A glucose tolerance test was normal. The haemoglobin, cell count, and prothrombin, clotting, and bleeding times were all normal.

For the first few days after admission the baby continued to pass streaks of blood in the stools. He remained difficult to feed with intermittent vomiting and no weight gain. The jaundice gradually faded and by the age of 1 month had clinically disappeared. The reducing substance persisted in the urine and the liver and spleen remained enlarged. Galactosaemia was suspected but chemical tests, such as the mucic acid test and the ozazone, were inconclusive. At this stage the eyes were examined by Mr. J. Minton who reported that there was a very small lens opacity in the posterior capsule of the right eye, and a small central lens opacity of the left eye.

At 1 month old when he was 6 lb. 12 oz. (8 oz. under

his birth weight) he was placed on a lactose-free diet as follows:

Casilan	g. 20
Glucose	g. 33
Olive oil	g. 18 (as emulsion)
Hartmann's solution	5 oz.
Salt mixture ..	(KH_2PO 6·1 g., mag. sulphate 4·08 g., ferrous sulph. 0·2 g., water to 1,000 ml.) = 50 c. cm.
Water to	20 oz.

This gave a feed of approximately 3·4% protein, 5·5% carbohydrate, and 3% fat. Later butter, ¾ oz., was emulsified as a substitute for olive oil.

Within 48 hours of starting this diet the reducing substance had completely disappeared from the urine. One week later the liver had receded to one fingerbreadth below the right costal margin and the baby was taking feeds well and was gaining weight slowly.

At 14 weeks the baby had a convulsion. There were clonic movements of the face, arms and legs with the wrists held in carpal spasm. Chvostek's sign was negative. He continued to have further mild attacks of twitching which were partially controlled by anti-convulsants, and, although not severe, persisted for about 2 weeks. The convulsions ceased after the baby was placed on mixed feeding. This suggests a possible metabolic cause for the fits. Serum chemistry at this time was persistently normal. From this point the baby progressed slowly apart from intermittent vomiting.

At 5 months old he failed to follow objects with his eyes and made no attempt to grasp objects. At 7 months he was taking an interest in his surroundings but was making no attempt to sit up. At 8 months Mr. Macauley reported that the right lens had a disc-shaped central opacity and the left eye punctate opacities. At 9 months he reported that the left lens opacities had cleared. At 10 months the baby could hold his head up well and he was able to fix well with his eyes. By 11 months he was able to sit up, and at 14 months he was following objects with his eyes and grasped objects with his hands.

At 21 months a liver biopsy was performed and was reported as being normal by Dr. N. E. France.

At 2 years old the child was walking well round his cot and was laughing and playing but he made no attempt to speak. At this time he was transferred to University College Hospital for the confirmation of the diagnosis and an assessment of the severity of the condition.

At the age of 3 years he weighs 26 lb. 4 oz. and his height is 33½ inches. He is making fair progress physically.

Dr. A. H. Bowley reports as follows on his mental development:

'His speech is very limited, consisting of a few words only. He vocalizes well, vowel and labial sounds especially. He screams when frustrated. He walks well and enjoys exploring, but prefers to crawl or hitch round on his buttocks. As regards his motor coordination, he has difficulty in holding a cup and could not fit round pegs in holes. As regards his adaptive behaviour, he fails to follow instructions to build a block tower, or to replace blocks in a box, or to fit nested boxes together, or to do up loose buttons, or to respond to mirror image verbally. He shows an interest in test materials, handles, sucks, and throws or bangs them to make noise. As regards his social behaviour, he responds to a stranger, accepts friendly advances of older children in the ward, does not appear to know his mother who visits him infrequently, and fails to imitate action suggested by an adult. Bowel and bladder control are not yet achieved. The achievement and skills of this boy are barely equivalent to those of a normal 18-month-old child, and his effective intelligence at present appears only that of a feeble-minded child.'

Discussion

The diagnosis of galactosaemia in this case was presumed at 1 month old from the clinical picture, namely lethargy, failure to thrive, vomiting, jaundice, hepatomegaly, cataract, and a reducing substance in the urine which disappeared on a lactose-free diet.

It has been suggested that if treatment is instituted early the manifestations of the disease are largely reversible. This appears to be so as regards the hepatomegaly and cataract, but it is doubtful if the mental retardation responds in the same way or if it depends on the same factors. The occurrence of mental defect is the most serious manifestation of the disease and it is important to determine whether it is an integral part of the syndrome or a complication of the metabolic disorder. From the literature it is difficult to assess the exact mental state of many of the cases reported.

Goldbloom and Brickman (1946) reported two cases, one of which showed no mental retardation, and they quoted a case of Norman and Fashena (1943) where the mentality was normal. In these cases treatment was started early, at 3½ months and 11 weeks respectively. They suggested that the mental retardation was not an associated congenital defect but the result of interference by the galactosaemia with the supply of glucose to the brain tissue or a direct toxic effect of galactose.

On the other hand a case reported by Townsend, Mason and Strong (1951) was treated within a few days of birth and remains mentally retarded. As already stated the case reported in this paper was on a lactose-free diet from 1 month old (apart from a period of 14 days at 2 years old for re-assessment) and yet is severely mentally deficient. It is admitted that the lactose-free diet contained 'casilan' and we note that Komrower and Holzel in a letter to the *British Medical Journal* of October 2, 1954, state that the small quantity of lactose in 'casilan' is excessive for such infants. They draw attention to three

infants treated early with 'correct dietary measures' where the mental and physical development was normal. It is not stated at what age the mental assessment was made or the pattern of social behaviour they exhibited.

In the case reported here there are various possibilities for the mental retardation.

Parental Background. The father's mentality is unknown. The mother has not been definitely assessed, but judging from correspondence from her her scholastic attainments are poor. Socially she is a pleasant and amiable person, going out to work and earning her own living. She is concerned about the child's welfare and shows appreciation of the efforts made on his behalf. She appears to be in the 'dullard' group, just below the limit of average intelligence.

Convulsions. The child suffered from convulsions at 3½ months old, and it is possible that these may have been a factor in his mental retardation. However, the convulsions were never severe and have not recurred.

Effect of Hospital. The child has been in hospital since birth and has therefore lacked the benefit of the stimulation he might have received in a good home. On the other hand he has had more attention from sisters, nurses and doctors than the average hospital patient, and we consider his degree of retardation too great to be attributed to deprivation of adequate stimulus alone.

Effect of the Disease Itself. Mason and Turner (1935) found that a high blood galactose depressed the blood glucose and suggested that the derangement in tissues other than the liver might be due to the continuous hypoglycaemia. One case reported by Townsend, Mason and Strong (1951) had hypoglycaemic shock after ingestion of galactose. Bruck and Rapoport (1945) criticize the hypoglycaemic hypothesis and point out that hypoglycaemia *per se* (for example, in glycogen storage disease and hyperinsulinism) does not produce similar symptoms.

If a toxic effect of galactose or a resulting hypoglycaemia were the direct cause of the mental defect the action would appear to be very selective as there is no evidence of permanent damage to other parts of the central nervous system.

Although the weight of evidence so far supports the view that the mental defect is of a secondary nature, a study of many more cases is needed before the possibility of a genetic origin of the retardation independent of the metabolic disorder can be ruled out. In subsequent studies of the condition, especially in those diagnosed and treated early on a diet completely free from lactose, we would urge a close study of the mental development, not only as regards an intelligence quotient, but also with a view to assessing the temperamental, adaptive and social behaviour.

We would like to record our thanks to Dr. C. E. Dent for his valuable help, and to Dr. A. H. Bowley for her assessment of the patient's intelligence.

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THE AMINO-ACIDURIA IN GALACTOSAEMIA

BY

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Excessive quantities of amino-acids have recently been found in the urine of infants with galactosaemia (Holzel, Komrower and Wilson, 1952; Bickel and Hickmans, 1952). At first sight, the occurrence of amino-aciduria in a condition known to be associated with severe liver damage would suggest that the amino-aciduria is of the 'overflow' variety, namely, that it occurs as the result of a rise of plasma level due to impaired deamination by the liver. However, the pattern of amino-acid excretion in galactosaemia does not resemble that of the already known overflow amino-acidurias of hepatic origin (Dent and Walshe, 1951). Moreover, preliminary investigations suggest that the mechanism is a renal one, presumably due to diminished tubular reabsorption of amino-acids by the kidney (Komrower, 1953). This is an interesting possibility since renal dysfunction has not previously been detected in this disease.

We describe here some investigations on a case of galactosaemia, a boy of 2 years who had been on a galactose-free diet from the age of 1 month. It was desired to reassess his tolerance to galactose with a view to possible modification of his very restricted diet, and this gave us the opportunity to investigate further the mechanism of the amino-aciduria under carefully controlled conditions.

Case Record

The full clinical record of this case is to be found on page 147. The patient had been under the care of Dr. Potter at the Queen Elizabeth Hospital for Children, and we are indebted to him for the opportunity to make this investigation. He was diagnosed as a case of galactosaemia at the age of 1 month and since then had been on a galactose-free diet. He was transferred for the purpose of this study to the Metabolic Ward, University College Hospital. On admission (September 10, 1953) he was 2 years of age, weighed 9·2 kg. and presented no abnormal physical signs but was somewhat backward mentally. His plasma urea was 42 mg./100 ml. and uncorrected urea clearances (UV/P) were 13·9 and 12 ml./min. The urine then contained no protein or reducing substances and the amino-acid chromatogram showed no amino-aciduria, the pattern of amino-acid excretion being the 'glycine pattern', the commonest of the normal variants (Dent and Walshe, 1954). A galactose tolerance test gave the results shown in Fig. 1.

He continued on the galactose-free diet which he had been having at the Queen Elizabeth Hospital, and from September 12, 1953, the quantity of the diet was carefully standardized. This intake was exactly maintained throughout the patient's stay in the ward.

The diet comprised:

GALACTOSE-FREE DIET
(Total calories 1,150)

		Protein (g.)	Fat (g.)	Carbohydrate (g.)
6 *a.m.* ..	150 ml. 'special milk'* ..	6·5	—	12·0
Breakfast	30 g. bread	2·5	0·4	16·7
	10 g. butter	—	8·5	—
	1 boiled egg	6·0	6·0	—
	150 ml. 'special milk'* ..	6·5	—	12·0
10 *a.m.* ..	150 g. orange juice	0·9	—	14·1
	10 g. glucose	—	—	10·0
Dinner ..	40 g. minced meat	7·7	4·2	—
	50 g. steamed potato mashed	0·7	—	9·9
	5 g. margarine	—	4·3	—
	30 g. steamed cauliflower ..	0·5	—	0·4
	50 g. apple (stewed) ..	0·2	—	6·1
	7 g. glucose	—	—	7·0
	150 ml. 'special milk'* ..	6·5	—	12·0
Tea ..	30 g. bread	2·5	0·4	16·7
	10 g. butter	—	8·5	—
	15 g. finely cut chicken ..	3·9	1·6	—
	2 g. marmite	—	—	—
	150 ml. 'special milk'* ..	6·5	—	12·0
Supper ..	50 g. pears (stewed) ..	0·2	—	5·4
	7 g. glucose	—	—	7·0
	150 ml. 'special milk'* ..	6·5	—	12·0
		57·6	33·9	153·9

* The special milk comprised 36 g. of 'casilan' (calcium caseinate), 60 g. of glucose, made up to 750 ml. with tap water. (Komrower and Holzel have recently stated in a letter to the *British Medical Journal* of October 2, 1954, that 'casilan' contains small quantities of lactose.)

From September 18, 1953, he was given, in addition to his standard diet, 20 g. galactose daily, taken divided with the meals. This quantity was chosen as being approximately the amount in the 1 litre of milk which a child of this age might be expected to consume. This was continued until October 2, 1953, after which the galactose supplement was omitted.

A few days after the galactose was begun the patient

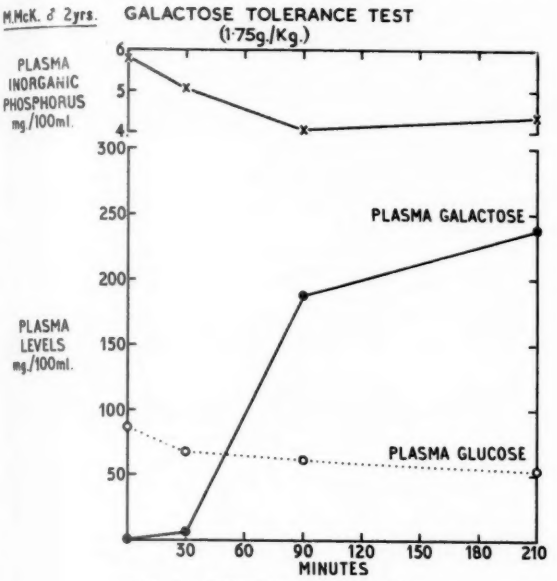

FIG. 1.—Galactose tolerance test.

became fretful and much more difficult to feed, and a week later some vomiting occurred which did not, however, persist. On withdrawing the galactose all his symptoms rapidly disappeared. Slight enlargement of the liver was detected after a few days; this disappeared later on returning to the galactose-free diet. After about four days on galactose a strong 'garlicky' smell appeared in his breath; this disappeared a few days later even though still taking galactose. On September 25 (eighth day of galactose) the 24-hour urinary excretion of galactose was 4·67 g., equal to 23·4% of intake. On September 28 (eleventh day of galactose) serum flocculation tests showed: Colloidal red, weak positive; cephalin cholesterol, weak positive; thymol turbidity, 9 units with flocculation. Serum electrophoresis showed a normal pattern except for a slight increase of γ globulin. Unfortunately the flocculation tests and electrophoresis were not done in the control period. Rather surprisingly, body weight was well maintained during the whole period of his time in the ward. He weighed 9·9 kg. when the investigation was completed on October 11.

Methods

Collection of Urine. It was not possible to collect continuously 24-hour urines from the patient. Clearance determinations were, therefore, done entirely on timed specimens collected in each case over the same period of the day. With a nurse in continuous attendance, two consecutive accurately-timed urines were collected, each of about one and a half to two hours' duration, with a blood specimen at the approximate mid-point of each urine collection. The urine collector described by Black (1951) was used. The specimens for clearance determinations were obtained on admission and on two further occasions towards the end of the galactose supplement. We unfortunately could not obtain further clearance data during the final control period as the patient developed a sore which prevented us from using the urine collector.

As frequently as possible throughout the period of his stay, spontaneously passed, untimed urine specimens were also collected. These were used for sugar and amino-acid chromatograms and for the determination of amino-nitrogen indexes.

Biochemical Analyses. Plasma and urine α-amino-nitrogen concentrations were determined by the methods of Hamilton and Van Slyke (1943) and Van Slyke, MacFadyen and Hamilton (1943) respectively. α-Amino-nitrogen clearances (uncorrected for surface area) were calculated on the Van Slyke formula UV/P. The urine α-amino-nitrogen excretion was also calculated whenever it was possible on the basis of the α-amino-nitrogen

$$\frac{\text{α-amino-nitrogen}}{\text{total nitrogen}} \times 100$$

indexes (Dent, 1947, 1954).

All our urine amino-acid chromatograms were prepared using phenol-ammonia and collidine-lutidine-diethylamine as solvents (Dent, 1948), mostly in the apparatus of Datta, Dent and Harris (1950). The volume of urine applied to each 20 cm. by 20 cm. square contained 150 μg. of total nitrogen (e.g., 15 μl. for urine containing 1% total nitrogen). At the time of applying the urine to the square, 5 μl. of 0·01 M α-amino-octanoic acid was also added to act as position marker. The strengths of the final spots were assessed on an arbitrary scale of 10 units (Dent, 1947). For better identification of amino-acids, selected urines were also analysed on large (18 in. by 22 in.) chromatograms, using the volume containing 250 μg. total nitrogen.

The general method of Horrocks and Manning (1949) was used for one-way chromatograms of urine sugars. The solvent used, however, was a butanol-pyridine-water mixture (Hough, Jones and Wadman, 1950).

Plasma galactose and glucose concentrations were determined in duplicate on specimens of venous blood collected into fluoride. Total plasma-reducing power was first determined in the usual way by the Hagedorn-Jensen method. The value for plasma glucose was obtained by subtracting from this figure the plasma-reducing power after incubation with yeast (Maclagan, 1940). The plasma galactose was determined from the plasma-reducing power remaining after fermentation. This was done by constructing a calibration curve for the final Hagedorn-Jensen thiosulphate titration from galactose solutions of known strength.

Urine galactose was determined by the standard Benedict method, using the factor for the reducing power of galactose, chromatograms having shown the absence of other reducing substances.

Results

The detailed findings are given in Table 1 and are summarized in Fig. 2. For purposes of comparison, urine α-amino-nitrogen indexes on five normal children aged 2-8 years are given in Table 2 as most previous work using this index has been on adults.

TABLE 1

Date	Stage of Investigation	Urine Flow (ml./min.)	α-Amino-nitrogen			Urea		Galactose	
			Plasma (mg./100 ml.)	Clearance (ml./min.)	Urine Index	Plasma (mg./100 ml.)	Clearance (ml./min.)	Plasma (mg./100 ml.)	Clearance (ml./min.)
Sept. 14	Control period	0·98	3·33	0·63	0·58	42	13·9		
		0·78	3·34	0·48	0·70	42	12·0		
Sept. 18	Control period				0·52				
Sept. 28	11 days on galactose	0·27	4·00	1·81	1·69	45	17·9	43*	9·65
		0·30	4·61	1·82	2·22	42	19·1	55*	9·85
Oct. 2	15 days on galactose	0·34	5·53	2·06	3·30	51	13·0		
Oct. 7	5 days after galactose was stopped				1·03				
Oct. 10	8 days after galactose was stopped				0·62				

* Corresponding plasma glucose concentrations 95 and 67 mg./100 ml.
Plasma α-amino-nitrogen values are corrected for plasma urea. All clearances calculated from formula UV/P. Only one plasma specimen could be obtained on October 2.

The figure is self-explanatory except for the curve showing the amino-aciduria. The units taken for this represent the summation of all the colour values (on our arbitrary scale) of ninhydrin reacting spots. Photographs of chromatograms taken throughout the period of the investigation show in more detail the urine amino-acid changes actually taking place (Fig. 3). A large chromatogram of the urine on October 2, 1953, when the strongest amino-aciduria was occurring, showed the typical galactosaemic pattern, namely, a relatively large increase in the small-molecular weight amino-acids especially serine, glycine, threonine and alanine, with lesser increases in glutamine, valine, the leucines and tyrosine. It may be that the amino-aciduria would become stronger if the galactose were taken for a longer period. The pattern is, however, very similar to that already illustrated for the two cases described by Holzel *et al.* (1952). The pattern illustrated by Bickel and Thursby-Pelham (1954) for the urine of a galactosaemic child shows certain differences, notably a relative increase in aspartic and glutamic acids and a decrease in glutamine. These differences could be due to artifacts of urine storage, as we have considerable experience of such changes occurring in stored specimens and appear to have produced a similar artifact, the increase of glutamic acid, in the specimen of October 2 shown on Fig. 3.

In every case when the urine reduced Benedict's reagent (Fig. 2), this was shown by paper chromatography to be due to galactose alone.

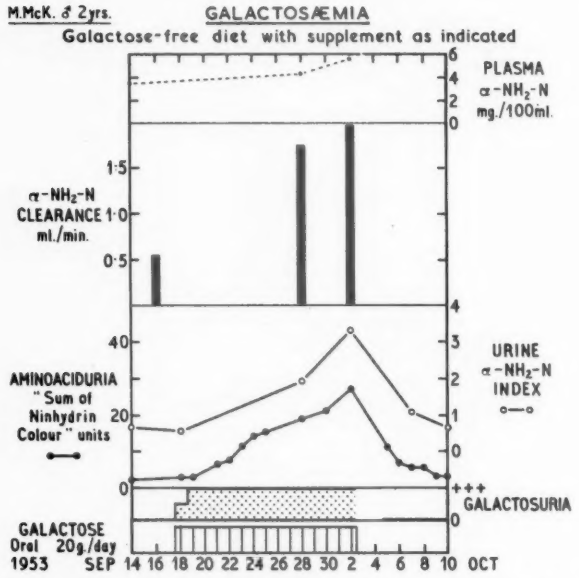
M.McK. ♂ 2yrs.
GALACTOSÆMIA
Galactose-free diet with supplement as indicated
PLASMA α-NH2-N mg./100ml.
α-NH2-N CLEARANCE ml./min.
AMINOACIDURIA "Sum of Ninhydrin Colour" units
URINE α-NH2-N INDEX
GALACTOSURIA
GALACTOSE Oral 20g./day
1953 SEP 14 16 18 20 22 24 26 28 30 2 4 6 8 10 OCT

FIG. 2.—Amino-acid clearances and excretions before, during and after addition of galactose to the patient's diet.

TABLE 2
URINE α-AMINO-NITROGEN INDEXES OF NORMAL CHILDREN

Subject*	Age	Sex	Index
C.	$2\frac{1}{12}$	F.	1·77
Sa.	$4\frac{5}{12}$	F.	1·46
T.	6	M.	1·10
Su.	$7\frac{4}{12}$	F.	0·96
A.	$8\frac{7}{12}$	F.	1·34

* All are siblings.

Discussion

Galactosaemia is a condition in which a precise clinical picture is associated with a defect in which the patient's ability to metabolize galactose is grossly impaired. It is of interest that two patients have been described who appear to have developed increased tolerance when they were examined at the age of 7 years (Townsend, Mason and Strong, 1951; Bray, Isaac and Watkins, 1952). It can be seen,

however, from Figs. 1 and 2 that our patient was still grossly intolerant of galactose at the age of 2 years after having been kept for nearly all this time on a galactose-free diet. He clearly needs to be maintained for a much longer period on this diet.

We must stress that the block in galactose metabolism was not complete, as also found by other workers, since our patient's 24-hour urine output of galactose was only 23% of his intake on the occasion we determined it. There was also a fall in plasma inorganic phosphorus during his galactose tolerance test (Fig. 1)—indirect evidence that he was then rapidly forming glycogen from circulating galactose and glucose. Like other workers we have also noted hypoglycaemia whenever plasma galactose was raised, and consider this a possible cause of the mental retardation and other symptoms, as originally suggested by Mason and Turner (1935).

The summarized results in Fig. 2 show that immediately after taking galactose by mouth a heavy galactosuria was induced. We presume that this disappeared equally rapidly when the galactose was discontinued, although unfortunately we were unable to obtain urine specimens until the third day after the galactose had been stopped. The galactose also induced a marked amino-aciduria, as has been found by other workers. The development of this, however, was slow in comparison with that of the galactosuria; indeed the amino-acid excretion was still increasing slowly on the fifteenth (and last) day of galactose administration. Not only did it take longer to appear, but also to disappear, for the urine amino-acid excretion did not return to normal until seven days after withholding galactose (Fig. 3). These changes were detected clearly by our arbitrary measurement of ninhydrin colour on the chromatograms and by the more accurate quantitative measurement of α-amino-nitrogen indexes (Fig. 2).

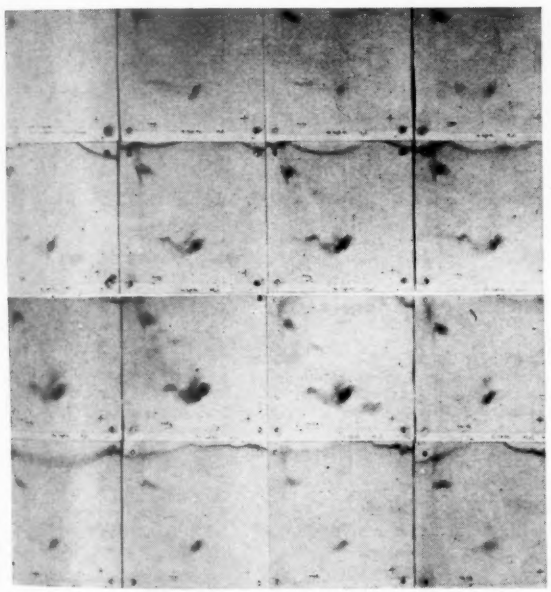

FIG. 3.—Photographs of serial chromatograms carried out during the course of this investigation.

Each square represents the small chromatogram carried out on the patient's urine as described in the text.

From left to right the dates of the urine collections are as follows: September 14 and 18, 1953 (galactose addition to diet begun on 18th); September 19, 21, 22, 23, 24, 25, 28, 30, October 2, 1953 (after October 2 galactose was stopped); October 5, 6, 7, 8, 10, 1953.

The onset and disappearance of the amino-aciduria a few days after the beginning and ending of the galactose addition are readily seen as a strengthening and increase in number of the amino-acid spots. Identifications of the amino-acids were done on larger chromatograms than these as the spots are less well defined on small chromatograms. The spot on the top left-hand corner of each square is due to α-amino-octanoic acid, added as a marker.

As far as the mechanism of the amino-aciduria is concerned, the clearance measurements (uncorrected for body size) show a marked rise in α-amino-nitrogen clearance of from 0·5 ml./min. in control periods to 2 ml./min. at the height of the amino-aciduria. This is clearly the main cause of the amino-aciduria, and, in the absence of comparable changes in the simultaneous urea clearances, it is almost certainly due to diminished renal tubular reabsorption of amino-acids. There was a slow rise in the plasma α-amino-nitrogen also, though the level never exceeded the upper limit of normal. However, as the patient was so carefully controlled as to dietary intake it is possible that the rise is significant and an indication of some slight degree of liver damage. It could contribute to the amino-aciduria, but only in small part, as normal subjects fed casein to produce similar slight rises in plasma level showed only a very slight rise in α-amino-nitrogen clearance (Dent and Fowler, 1954, and further unpublished work). Bickel and Thursby-Pelham (1954), however, found grossly raised plasma α-amino-nitrogen levels of 8·3 and 8·8 mg./100 ml. in their case. We have never found such high values in cases of galactosaemia, and, in fact, have only encountered such figures in terminal cases of liver disease, and then only when there is almost complete destruction of the liver parenchyma.

A further argument against the possibility that liver damage contributes appreciably to the amino-aciduria concerns the pattern of urinary amino-acid excretion found in these cases. In mild liver disease of various aetiologies, the amino-aciduria mainly comprises relative increases in some of the following amino-acids and closely related compounds: cystine, taurine, β-amino-isobutyric acid, methylhistidine, ethanolamine and methionine (Den and Walshe, 1951; Walshe, 1953). Such was no

the case with our patient nor with those of Holzel *et al.* (1952).

It is interesting to compare and contrast the mechanisms of the galactosuria and of the amino-aciduria. The galactosuria occurred as soon as the plasma galactose level was raised and stopped as soon as the level returned to normal, strongly suggesting that it resulted from the rise in plasma level. The amino-aciduria, on the other hand, was probably due to some chemical ('toxic') action on the renal tubular cells—possibly due to galactose itself—several days being required to produce and to recover from this 'toxicity'. This would account for the failure to observe amino-aciduria in galactosaemic patients maintained on a galactose-free diet when they are given galactose on one day only (Bickel and Hickmans, 1952; Bickel and Thursby-Pelham, 1954).

Galactosaemia is now believed to be an inborn error of metabolism. If this is so, we must postulate here that the amino-aciduria is not a direct effect of the abnormal gene, as for instance is the case in cystinuria and in some other inborn renal tubular reabsorption abnormalities, such as β-amino-isobutyric aciduria (Crumpler, Dent, Harris and Westall, 1951; Harris, 1953). The amino-aciduria of galactosaemia must be a later change induced by the primary abnormality and is therefore somewhat akin to the amino-aciduria which occurs in patients with Wilson's disease. This latter amino-aciduria (as also the other signs of the disease) does not appear to be present from birth but to result from the action over many years of an environmental factor to which they have an inborn sensitivity and which is in Wilson's disease presumably an intoxication by dietary copper. We think it is highly significant that a delay in appearance of the amino-aciduria in a case of the Fanconi syndrome has also been recently described (Bickel and Thursby-Pelham, 1954). It is well known that the other signs and symptoms of this syndrome show a similar delay in onset.

Summary

A boy of 2 years of age with galactosaemia has been studied.

He had an abnormal galactose tolerance curve after having been nearly two years on a galactose-free diet.

Under carefully controlled conditions, he was given 20 g. a day of galactose by mouth for 15 days. The amino-aciduria slowly developed while he received the galactose and slowly disappeared after it was stopped.

The amino-aciduria occurred mainly as a result of decreased renal tubular reabsorption of amino-acids.

We wish to thank Sister C. Turner for supervising the nursing arrangements, Miss D. Tuck for preparing the diet, and Drs. J. Anderson and B. Senior for medical assistance. We also thank Mr. V. K. Asta for the diagrams, and Mr. Q. Bligh for the photographs.

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A STUDY OF THE GENETICS OF GALACTOSAEMIA

BY

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The medical world, of recent years, has shown an increasing interest in the hereditary metabolic disorders and considerable research has been undertaken in an endeavour to follow the physical and biochemical problems involved. It is generally accepted that both the presence and absence of enzymes or enzyme functions are determined genetically, but it is not yet known whether a single gene, the specific unit of heredity, is responsible for a single or for several enzymes. It is most probable that the capacity for a definite enzyme reaction is inherited as a dominant characteristic, whereas its absence is likely to be of a recessive nature.

Harris (1953), in his *Introduction to Human Biochemical Genetics*, pointed out that in 1923 Garrod had put forward the hypothesis of congenital absence of a certain enzyme (or enzymes) leading to a block in the chain of metabolic reactions and that by careful examination of the individual stages it should be possible to trace the faulty link. This conception of metabolic blocks has therefore opened up a new and promising line of research into both genetics and biochemistry.

Galactosaemia, a disease which recently has attracted a great deal of attention, has been known to occur in more than one sibling of a family, but its mode of inheritance has been a matter of speculation. Up to the present no special techniques have been consistently employed by which one could recognize the specific trait, if present, in clinically unaffected members of the families in which cases of the disease have been found. Göppert (1917) was the first to note the familial incidence of galactosaemia, though he established the diagnosis beyond doubt in only one case. The medical history of the three other siblings made it more than likely that they also suffered from the same inborn error of metabolism. Bell, Blair, Lindsay and Watson (1950) mention its occurrence in two siblings. Donnell and Lann (1951) report the disease in three siblings; after having recognized it in the youngest they diagnosed it retrospectively in the two others. Townsend, Mason and Strong (1951) described among their six cases two siblings with galactosaemia, while the third child of the same parents seemed entirely normal though she gained weight slowly. The authors point out that theirs is the first record of a family where the disorder existed in two siblings but not in the third. They had not, however, examined the third child's response to a galactose tolerance test. Gorter (1951) gave a short account of familial galactosaemia, but the available data were incomplete. Hudson, Ireland, Ockenden and White-Jones (1954), reporting four cases, found the disturbance in two siblings, but in one it was assumed on retrospective evaluation of the case history; the mother of these children later gave birth to binovular twin boys who have remained healthy. Cox and Pugh (1954), in a communication on six cases, found three in one family and two affected siblings in a second. Three of the cases again were diagnosed in retrospect only. Consanguinity in the parents of proven cases of the disease has not yet been commented upon in the literature.

Between May, 1951, and April, 1954, five cases of galactosaemia came under our observation. They occurred in four families, were clinically typical, and in each case the diagnosis was confirmed by the isolation of galactose in the urine and by the presence of significant levels of this sugar in the blood. The galactose tolerance tests carried out in four of the patients were grossly abnormal, the fifth child dying before the investigation could be undertaken. (Details of the case histories will be discussed elsewhere.)

The galactose tolerance test, although not specific, is regularly and persistently abnormal in cases of galactosaemia, even when the active phase of the disease has long since abated, either spontaneously in the milder forms or on milk-free diets in the treated. For these reasons it was decided to use this technique in an attempt to study the genetics of the condition.

Following a preliminary clinical examination to exclude other causes of galactose intolerance (such as liver disease) the test was carried out on as many relatives of the patients as agreed to submit to it.

TABLE 1
GALACTOSE TOLERANCE TESTS ON THE FAMILIES OF CASES OF CLINICAL GALACTOSAEMIA

	0 hr.	½ hr.	1 hr.	1½ hr.	2 hr.	Index	
Family F.							
H.F. (father)	0	60	133	98	33	324	1 proven case of galactosaemia, 1 likely case
F. (mother)	0	25	48	52	0	125	
M.F. (grandmother)	0	40	65	5	0	110	
A.F. (brother)	0	52	72	68	30	222	
L.F. (uncle)	0	84	57	38	33	212	
M.F. (cousin)	0	48	64	73	10	195	
A.G. (aunt)	0	30	55	30	10	125	
Family K.							
M.K. (father)	0	105	85	25	10	225	1 proven case
W.K. (mother)	0	10	55	65	60	190	
Family G.							
G. (father)	0	25	40	48	58	171	2 proven cases
G. (mother)	0	16	37	4	0	57	
J.G. (brother)	0	42	45	0	0	87	
W.G. (sister)	0		Traces only		0	—	
Family S.							
R.S. (father)	0	43	83	42	0	168	1 proven case
S. (mother)	0	15	60	47	13	135	
R.S. (brother)			Traces only				
Family L.							
L. (father)	0	38	32	20	0	90	2 probable cases
L. (mother)	0	230	60	78	38	406	
L.L. (sister)	0	30	40	190	100	360	
E.L. (sister)	0	10	58	134	130	332	

Adults were given a total dose of 40 g. of galactose, and older children were given 1·25 g. and infants 1·75 g. per kg. body weight. The determination of the galactose in the blood was made by the method of Maclagan (1940). The galactose index is the sum of the half-hourly blood galactose values up to two hours expressed in milligrams per 100 ml. after the ingestion of galactose; the index is of little use in children. With the 40-g. dose in adults the average normal value is 68 with an upper limit of 160. The galactose tolerance test was regarded as normal if the blood galactose values returned to the fasting level within two hours and in adults the galactose index did not exceed 160. Table 1 gives the results obtained in testing the relatives of the galactosaemic patients. It shows that in each family at least one parent reacted abnormally to the galactose tolerance test; the figures also reveal many instances of an abnormal galactose index in other relatives, who had no clinical manifestations of the disease, although in some of the individuals concerned there was a history of feeding difficulties in early infancy.

The family trees of the galactosaemic patients are presented in Figs. 1, 2, 3 and 4. They were computed on the basis of the test findings.

Family F. (Fig. 1)

In addition to the patient, who is now a healthy, active girl of 3 years of age, there was a second female sibling who died aged 11 days of an illness which in retrospect has been diagnosed as galactosaemia. The third child, a boy, as well as the father, uncle and cousin, have abnormal galactose tolerance curves.

Family K. (Fig. 2)

Both parents show abnormal tests; the patient is developing normally both physically and mentally.

Family G. (Fig. 3)

There were four siblings in this family. The first baby died of pneumonia at the age of 8 months; his history was typical of galactosaemia and on his admission to hospital he was found to excrete a reducing substance in the urine which was identified as galactose, but unfortunately too late to undertake any therapeutic steps. The second child was seen for the first time at the age of 3 years with fully developed cataracts, mental retardation and slight liver enlargement. Galactosuria was not present, but his galactose tolerance was greatly reduced. Two other children, a brother and sister, are perfectly healthy and have normal galactose tolerance tests, which, in the case of the father, is abnormal.

Family S. and Family L. (Fig. 4)

The father of the patient produced an only slightly abnormal response to the tolerance test, but on adding 30 g. of galactose daily to his normal diet, he developed nausea and vomiting within three days, as well as an irritating scaly rash of the face which subsided a fortnight after he ceased to take the additional galactose.

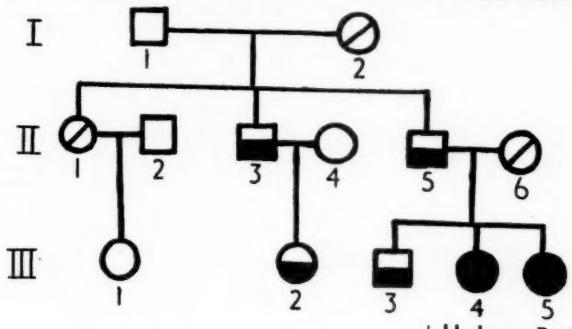


FIG. 1.

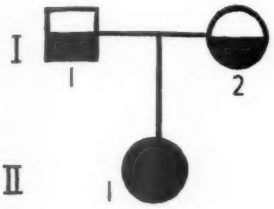


FIG. 2.

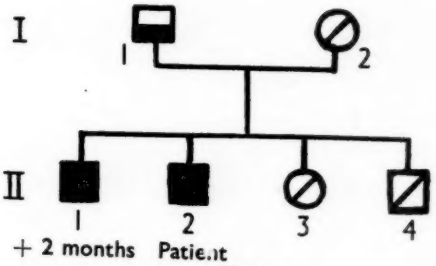


FIG. 3.

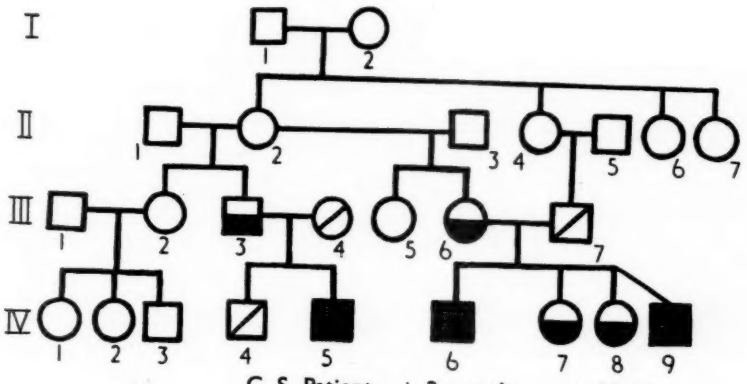
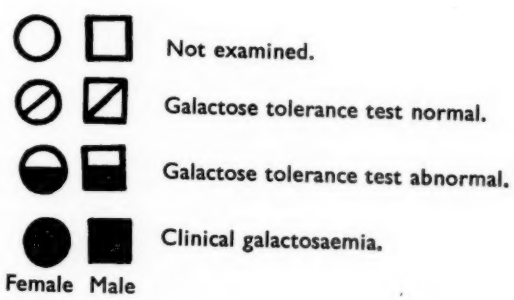


FIG. 4.



The results of the investigations on the other members of the family were normal and the patient, now aged 3½ years, is developing normally. The father's half-sister, an offspring of his mother's second marriage, married a first cousin (a son of her mother's sister).

Four children were born to these consanguineous parents. The first child died at the age of 2 months at the Royal Hospital for Sick Children, Edinburgh, 24 hours after admission. The history was characteristic, and Dr. Agnes Macgregor, after reviewing the morbid histology, wrote in a personal communication (1953) that there was no reasonable doubt that this was a case of galactosaemia. The next child, a girl, seemed to develop normally. Then followed a twin birth; the male infant died aged 18 days at the Doncaster Royal Infirmary, and again the history was in keeping with galactosaemia, while the other twin, a girl, developed normally. Galactose tolerance tests showed grossly abnormal curves for mother and both daughters, while that of the father was within normal limits.

Although the diagnosis in the dead siblings is one of probability only, it would appear justifiable to regard these cases as galactosaemia and therefore the first recorded in the offspring of consanguineous parents.

Discussion

Haldane (1954) expressed the opinion that galactosaemia is probably due to the inheritance of a recessive gene as did Penrose in a personal communication quoted by Hudson *et al.* (1954). If this is the case one would expect such a recessive Mendelian character to show two very distinctive features: first, a relatively high frequency of the condition among siblings of affected individuals and only rarely among their parents, children or more distant relatives; secondly, a higher number of consanguineous marriages among the parents of the cases than in the general population (Harris, 1953). The first of these postulates seems to be fulfilled in the reports published on the familial occurrence of galactosaemia. Consanguinity of the parents has, however, not been noticed previously and this single observation is inadequate to offer any foundation for a firm conclusion on the second point.

Using the galactose tolerance test as a screening technique it is only in the Family K that this method seems to reveal abnormal tolerance as a recessive trait. But, reviewing the findings in the members of the other four families, it immediately becomes obvious that reduced tolerance for galactose as revealed in the test is found in at least one parent of every child with clinical galactosaemia and, as seen in the Family F., in the more remote relatives. Although in the Family L. the parents are first cousins, only the mother and the surviving two children had abnormal galactose tolerance tests. This indicates that abnormal galactose tolerance without clinical manifestations is probably inherited as a heterozygous character, i.e., dominant. The individuals who develop the active overt form of the disease may be homozygous for the same gene, or there may be other factors that accentuate the condition.

Thalassaemia provides a comparable distribution of genetic factors. This form of haemolytic anaemia, which is due to a hereditary defect of haemoglobin synthesis, can be transmitted as a heterozygous dominant gene and individuals carrying it are clinically well but show characteristic blood changes. This subclinical form has been described as thalassaemia minor. The homozygous offspring of two parents with thalassaemia minor present more pronounced haematological changes accompanied by severe clinical manifestations and often succumb to the disease; this is thalassaemia major. Family K., where both the parents show marked abnormal galactose tolerance, offers itself readily for comparison.

This study has shown that the abnormal galactose tolerance factor is much more common than originally suspected and that it is likely to become more widespread. There is as yet no information available as to the presence of the disease in children of treated or untreated and surviving patients suffering from galactosaemia, but there is little doubt that with earlier diagnosis a much larger number of galactosaemic babies will remain alive, grow, mature and procreate, and it is likely that galactose diabetes will have to play a more important part in diagnostic considerations than heretofore.

Summary

Galactose tolerance tests carried out in members of five families in which cases of galactosaemia occurred showed a reduced tolerance for galactose in at least one parent as well as in other relatives of the patients.

In one family the parents were first cousins. Two siblings died of galactosaemia; two surviving children as well as the mother have a grossly abnormal galactose tolerance.

This is the first record of galactosaemia in the offspring of a consanguineous marriage.

It is concluded that abnormal galactose tolerance without clinical manifestations is inherited as a heterozygous character, while clinical galactosaemia

may be transmitted as a homozygous recessive gene.

We are greatly indebted to Mr. H. Varley, biochemist at the Manchester Royal Infirmary, and Dr. H. Lederer, pathologist at Doncaster Royal Infirmary, for carrying out the galactose tolerance tests on the relatives of our patients, and to Dr. Agnes Macgregor for reviewing the necropsy findings in one of the cases. Our special thanks are due to Dr. H. Harris, lecturer in biochemistry in the London Hospital Medical College, for his considered advice and most helpful criticism, and to Professor Wilfrid Gaisford for his unfailing interest.

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A FAMILIAL TUBULAR ABSORPTION DEFECT OF GLUCOSE AND AMINO-ACIDS

BY

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It has become increasingly clear in recent years that a group of disorders in childhood results from defects in reabsorption by the renal tubules. The common feature of these conditions is a failure to reabsorb adequately a number of substances which are filtered out of the blood by the glomeruli and which are present in the blood in normal concentrations. The substances include water, glucose, amino-acids, phosphate, chloride, bicarbonate, sodium and potassium ions.

While it is evident that many of these reabsorption defects may be acquired in the course of renal disease, a growing number of conditions have been described in which these appear in early childhood. Many are probably congenital. They are strikingly selective, and exhibit in most cases a strong familial tendency.

The best known of these conditions is renal glycosuria, in which a selective leak of glucose exists, transmitted as a Mendelian dominant gene. This is a benign and symptomless condition, which probably explains why it is frequently not discovered until adult life. Its occurrence in childhood and even in infancy is, however, well documented (Shafton and Poncher, 1934). A failure to reabsorb water gives rise to the condition variously termed 'nephrogenic diabetes insipidus' (Williams, 1946) or 'pitressin-resistant diabetes insipidus' (Dancis, Birmingham and Leslie, 1948), in which severe polyuria, polydypsia and dehydration fever are present from birth and soon become clinically evident. This condition also is familial (Williams, 1946), although its rarity has so far prevented more exact knowledge of the nature of the inheritance. Infantile renal acidosis is another example in which the reabsorption of basic and bicarbonate ions is impaired.

A tubular disturbance resulting in excessive loss of sodium and chloride ions sometimes develops in cases of chronic nephritis. This condition, 'salt-losing nephritis', was first described by Thorn, Koepf and Clinton (1944), and has so far been seen only in adults. It is tempting to speculate that it will one day be discovered in childhood as a congenital tubular disturbance, causing dehydration and inanition.

This paper is concerned particularly with failure of glucose, phosphate, and amino-acid reabsorption. These abnormalities are frequently associated with each other, perhaps because all these substances are reabsorbed in the proximal tubule (Richards, 1938; Stowers and Dent, 1947). A family is presented in which the reabsorption of glucose and amino-acids was interfered with, but not that of phosphate. No previous report has appeared of this combination of disturbances, which came to light because of moderate dwarfism in one of the patients.

Case Histories

Case 1. Lindsay B., aged 5, one of female twins, was brought for advice because of poor appetite, thirst and failure to grow. She had been miserable for the previous few months, and was sleeping badly.

She was the smaller twin at birth, having a birth weight of 4 lb. 15 oz., but apart from a slower growth and weight gain than her twin her early history was uneventful. There were no previous illnesses. The parents were both well and of normal height and appearance, but there was a history that the paternal grandfather had died of an illness resembling diabetic coma after having been found in earlier years to have sugar in the urine.

On examination the patient was a considerably stunted, sallow and underweight child, who might have passed on appearance for a case of renal rickets except that she was vivacious and active, and showed neither knock-knee nor other skeletal deformities. Her height was 36 in. and weight 23 lb. 14 oz. Her intelligence was normal and no abnormalities were found in any system, including the genitalia and skeleton. In particular, there were no signs of rickets.

Blood analysis gave: Urea 29 mg. %, calcium 10·1 mg. %, phosphorus 4·2 mg. %, bicarbonate 45·0 vol. CO_2 %, chlorides 623 mg. % as NaCl, potassium 17 mg. %, sodium 345 mg. %, alkaline phosphatase 31·9 units % (King-Armstrong), sugar 73 mg. %, and *p*H 7·2 (at 37° C.).

Bone age measured at the wrist was 3-3½ years (lower limits of normal).

The urine was examined by paper chromatography and contained a small quantity of protein, glucose 0·5-2 g. %, fructose 25 mg. % and a gross excess of amino-acids. Proline, leucine and valine were most prominent, and cystine, lysine, tyrosine, serine, threonine, alanine, glutamine, beta-alanine, alpha-amino-butyric acid and methionine were also greatly in excess.

A glucose tolerance curve was normal.

Case 2. At this stage, the twin, Glenys, was admitted. This child had had no symptom or previous illnesses. Her birth weight was 5 lb. 15 oz. and she had always thrived rather better than her twin.

On examination she was a sturdy, cheerful child, somewhat taller and heavier than her twin. Her weight (32 lb.) was rather low for her age, but her height (40¾ in.) was within normal limits. No abnormal physical signs were found in any system.

Blood analysis gave: Urea 30 mg. %, calcium 10·2 mg. %, phosphorus 5 mg. %, bicarbonate 51·4 vol. CO_2 %, chloride 608 mg. % as NaCl, potassium 16·4 mg. %, sodium 330 mg. %, alkaline phosphatase 27·2 units % (King-Armstrong), sugar 82 mg. % and *p*H 7·2 (at 37° C.).

The urine showed traces of protein, but was otherwise normal.

A glucose tolerance curve was normal.

The urine was examined by paper chromatography and showed considerable excess of the same amino-acids as in the twin, and of glucose and fructose. All these substances were present in rather smaller amounts than in the twin. Some protein was also present.

Both Twins. Bone marrow smears showed no cystine crystals, nor were any seen on slit-lamp examination of the corneae.

Paper chromatography of blood showed that blood amino-acid levels were below normal, but the distribution patterns were normal.

Urinary nitrogen excretion was as follows:

Excretion (in 24 hr.)	Glenys	Lindsay
Total urinary nitrogen	5·64 g.	4·18 g.
Urea nitrogen	4·86 g.	3·38 g.
Ammonia nitrogen	252 mg.	200 mg.
Amino-acid nitrogen	396 mg.	276 mg.

The blood groups of the members of the family were as follows:

Twins	O IV	CDe/cde	Ns/Ns	P+	Lu−	K−	Le^a−	Le^b+	Fy^a−
Mother	O IV	cDE/cde	Ms/Ns	P+	Lu−	K−	Le^a−	Le^b+	Fy^a+
Father	O IV	CDe/cde	Ms/Ns	P+	Lu−	K−	Le^a−	Le^b+	Fy^a+

Parents. The mother showed no biochemical abnormalities in the blood or urine.

The father was a tall, well built man who looked and felt well, and was symptomless. His previous history contained nothing relevant. Apart from his father, his family history was also negative.

His urine contained an excess of glucose, fructose and amino-acids, in the same patterns as in the twins, but in rather smaller concentrations than in either of them. His blood amino-acid levels were below normal, but the distribution pattern was normal. His blood sugar, calcium, phosphorus and alkaline phosphatase levels were normal.

Paternal Grandfather. He was a very short, spare man, weighing about 7 stones. He was discovered in the late thirties to have glycosuria, which was investigated and found to be of renal type due to a low threshold. In his later years he suffered from intercostal neuralgia and arthritis of thoracic vertebrae 5-12. These vertebrae were osteoporotic and a diagnosis of Paget's disease was considered at one time. In 1945, at the age of 56, he complained of severe weakness after an emotional shock, and the discovery of sugar in the urine led to treatment by a diet which rendered his urine sugar-free. Ketosis developed and he died in coma.

Discussion

The presence of considerable amounts of glucose and amino-acids in the urine can be due only to a spill-over resulting from the failure of the renal tubules to reabsorb these substances entirely from the glomerular filtrate. When the renal tubules are functioning normally this can only occur when the glomerular filtrate concentrations of these substances rise above a certain critical level, that is, when the threshold of each is exceeded, but functional abnormalities of the tubules are found in which reabsorption fails in the presence of normal or even low glomerular filtrate concentrations. The thresholds in these cases are low. The normal blood glucose levels and tolerance curves, and the low blood amino-acid levels in our cases place them in the group of functional tubular failure causing low thresholds.

It is probable that normal tubular function is dependent on many influences. Harrison and Harrison (1941) showed that one of these influences is vitamin D. Deficiency of this vitamin, among other effects, diminishes the reabsorption of phosphate ions in the proximal tubule, resulting in phosphate leaking and low blood levels. This dysfunction is temporary, and is fully corrected by giving vitamin D. Glucose and amino-acids can be similarly affected in certain circumstances. Amino-aciduria in vitamin-deficiency rickets was reported by Jonxis, Huisman and Smith (1952). Vitamin D treatment greatly reduced but did not entirely abolish this amino-aciduria, and, in a later paper, Jonxis and Huisman (1953) reported that traces persisted in the urine of these patients. Since their report we have obtained similar findings in a case of vitamin-deficiency rickets.

Vitamin D deficiency rarely appears to upset

glucose reabsorption in children, but glycosuria is well recognized in adult osteomalacia (Albright and Reifenstein, 1948). Vitamin C was shown by Jonxis and Wadman (1950) to act in a similar way on the renal tubules, and a deficiency will aggravate the amino-aciduria of vitamin-deficiency rickets.

In addition, it has been shown that a number of substances can act as poisons to the renal tubules, producing glycosuria and amino-aciduria. These manifestations are well known in lead poisoning in man (Wilson, Thomson and Dent, 1953), and Spencer and Franglen (1952) found them in lysol poisoning. Animals poisoned experimentally with uranium also produce glycosuria and amino-aciduria (Voegtlin and Hodge, 1949-53), and it is probable therefore that a number of substances can act in this way.

The exact mechanism of the congenital and hereditary variety of this tubular disturbance is not known. Stowers and Dent (1947), reporting the pathological findings in a fatal adult case of the Fanconi syndrome, state that phosphatase was present in Henle's loops and the collecting tubules, but absent from the proximal tubules, the exact reverse of the normal position. Jackson and Linder (1953) suggest that this deficiency may be the primary cause of the failure of reabsorption, as glucose and amino-acids are normally phosphorylated before absorption. This would not, however, explain how the defect might involve any one of these substances, unless it be that there are separate phosphatases for each. It is held by Fanconi (1954) that a deficiency of carbonic anhydrase in the proximal tubule may be one of the possible mechanisms underlying infantile renal acidosis, by causing an insufficient release of hydrogen ions from bicarbonate, and it may be that many, if not all, congenital tubular dysfunctions result from enzyme deficiency or inefficiency.

The pathology of these conditions has naturally been studied extensively only in the more severe and rapidly fatal variations, particularly the Fanconi syndrome. Severe degenerative changes have been found consistently in the renal tubular epithelium, the changes being more marked in the proximal than in other parts of the tubule (McCune, Mason and Clarke, 1943; Stowers and Dent, 1947). These changes may consist of flattening or swelling of the epithelium, fatty deposits in the basal stratum, deposits of particulate matter, possibly cystine, in the tubule cells, or fibrosis. Darmady (quoted by Fanconi, 1954) has demonstrated cellular atrophy in the proximal tubules of cases of tubular insufficiency by dissection of individual nephrons. Stowers and Dent conclude that the various changes represent different stages of one process. The question of glomerular lesions in this group of conditions is more doubtful. The constant small amounts of protein in the urine of our cases suggests the possibility of such lesions, although the normal blood urea and phosphorus levels do not indicate any great severity. Slight albuminuria could also be explained by secretion from abnormal tubules. Assuming that our cases had their renal abnormalities from birth, the survival of the grandfather till the age of 56 and the good general health and normal blood chemistry of the father do not argue for glomerular lesions of any consequence. The cause of death of the grandfather, from the information available, suggests ketotic coma, possibly as a result of severe carbohydrate restriction, rather than renal failure. It is also noteworthy that many cases of the Fanconi syndrome survive to adult life. King and Lochridge (1951) found normal glomeruli in their case, and Stowers and Dent (1947) found only minor changes. It appears from a study of the literature that severe glomerular lesions occur most often in cases with multiple reabsorptive defects associated with cystinosis, and in only a proportion of these.

The proximal tubule reabsorbs glucose, amino-acids, most of the phosphate ions, water, sodium and chloride ions (Fanconi, Ruegg and Dieterle, 1951).

Considering the first three substances only, it will be seen that there are seven possible variations of reabsorptive deficiencies, as follows: (1) Glucose, (2) phosphate, (3) amino-acids, (4) glucose and phosphate, (5) phosphate and amino-acids, (6) glucose and amino-acids, (7) glucose, phosphate and amino-acids.

Of these, (1) is the well recognized condition of renal glycosuria; (2) is vitamin-resistant hypophosphataemic rickets; (3) occurs in a selective form in hereditary cystinuria (Dent and Rose, 1951), a condition in which cystine, lysine and arginine fail to be reabsorbed but a general amino-acid leak has not been reported in the absence of glucose or phosphate leak; (4) is a combination of glycosuria and hypophosphataemic rickets, and has been reported in a number of cases in the literature quoted by McCune *et al.* (1943); (5) is a rare combination but occurred in one of the cases reported by Jonxis and Huisman (1953). In a number of cases of rickets showing amino-aciduria, one was found to be of the vitamin-resistant hypophosphataemic type. Variant (7) occurs together with other features, such as potassium leak and cystinosis, in the Fanconi syndrome.

Variant (6) occurred in the family reported in this paper. The development of rickets in this type of

tubular disturbance appears to depend on whether phosphate leaks. No evidence of rickets could be found either radiologically or clinically in the twins, although the serum alkaline phosphatase levels were considerably raised in both. No certain explanation can be given for this finding at present. The possibility exists that the cause might lie in a disturbance of liver function. The work of Himsworth and Glynn (1944) has shown that a deficiency of cystine and methionine in the diet will lead to liver cirrhosis in rats. Hepatic lesions, comprising fatty infiltration, centrilobular necrosis and frank cirrhosis, occur in a high proportion of cases of the Fanconi syndrome (McCune *et al.*, 1943). The case reported by Stowers and Dent (1947) had gross cirrhosis, and several discrete areas of malignant hepatoma. It seems likely, therefore, that a persistent loss of methionine and cystine in the urine, leading to low blood levels, has the same effect as a deficiency of these amino-acids in the diet, but this cannot be regarded as the whole explanation of the hepatic lesions until further work has shown a close coincidence between those cases which lose methionine and cystine in the urine and those which have hepatic lesions. Methionine and cystine were passed in considerable excess in the urine of the twins, but for the present this explanation for the raised alkaline phosphatase levels is speculative.

It is interesting to consider the reason why one twin failed to grow as well as the other. A simple explanation would be that the twins were binovular, and this cannot be ruled out with absolute certainty. They do, however, bear a close facial resemblance (Fig. 1), and have identical ABO blood groups, rhesus genotypes and other associated cell factors. Having regard to the blood groups of the parents, the probability of their being identical twins can be stated as 64 : 1.

Quantitative estimations of the amino-acid nitrogen excretion in the urine show that the total output per 24 hours is of the order of 7% of the total daily nitrogen excretion, a figure which seems inadequate to cause any significant protein starvation. Were this amino-acid loss a causative factor, one would also expect the dwarfed twin to pass considerably more amino-acids than her sister, whereas she appears to pass approximately the same amount, or perhaps less. The chemical estimations must be regarded as being more accurate for quantitative purposes than the paper chromatography findings. An amino-acid nitrogen loss of 7% of the total nitrogen excretion is, however, quite abnormal. Bickel and his associates (1952) state that anything greater than 2% is pathological, and many of their cases had coefficients of over 10%.

FIG. 1.—The twins with normal control.

If, however, the total amino-acid loss seems unlikely to account for dwarfism, it is possible that the loss of those regarded as essential may do so. Threonine, valine, leucine, lysine and methionine, all of which were found in the urine of our cases, come into this category. We have no proof, however, that these are being lost in greater quantities in the dwarfed child than in her sister.

It can only be said at this stage that the same gene has acted with different force in the three generations, and in the two presumably identical twins. This phenomenon is well known in cases of hereditary cystinuria and the Fanconi syndrome, and Stowers and Dent (1947) offer the suggestion that more than one gene is involved in this group of tubular dysfunctions and that the subsidiary genes may alter the manifestations of the main gene.

Summary

The congenital defects of renal tubular function are discussed, with particular reference to disturbances of glucose, phosphate and amino-acid reabsorption.

A family is presented in which a defect in glucose and amino-acid reabsorption was transmitted as a dominant gene to three successive generations, the youngest of which consisted of twins. This particular defect is one of seven possible combinations

involving glucose, phosphate and amino-acids, and is likely to be symptom-free unless severe and persistent loss of essential amino-acids leads to stunting of growth.

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A CASE OF HYPOTHYROIDISM WITH NEPHROCALCINOSIS

BY

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Hypothyroidism is the commonest of all endocrine disorders in childhood. Its association with extensive nephrocalcinosis, however, must be very rare, and so the following case is of interest.

Case Report

A girl aged 4½ years was admitted to the Paediatric Unit, Clatterbridge Hospital, Bebington, Cheshire, on February 8, 1954. She had been taken to her family doctor for treatment of a furuncle below the right eye and he had referred her as a case of cretinism.

The child weighed 7½ lb. at birth and was born in West Kirby, Wirral. She was breast fed for one month and then the family moved to Scotland. She is the second child in a family of three. The siblings, a sister aged 6 years and a brother aged 2 years, are normal and healthy. The parents are well and there is no family history of goitre.

At the age of 3 months the mother noticed that the child had little interest in her surroundings and that she had a large tongue and a squint. At 9 months she started to hold up her head, and began to sit with support when 3½ years old. Her first tooth erupted at that time. She had always been constipated. Normal amounts of vitamin D in the form of cod liver oil and 'minadex' had been given.

When 10 months old, the patient was seen at another hospital and a diagnosis of mongolism was made. No treatment was advised and the parents accepted this opinion.

On admission to Clatterbridge Hospital she presented the typical appearance of hypothyroidism. She had dry, scanty hair, a dull expression, and a large protruding tongue. The abdomen was protuberant, the extremities blue and cold, the skin greyish, mottled, coarse and dry, and there was non-pitting oedema and myxoedematous firmness of the tissues. She was grossly stunted (height 26 in., weight 18½ lb., skull circumference 16½ in., abdominal girth 19½ in.) and the limbs were short. One upper and one lower incisor were erupting. She could smile and hold up her head and just sit with support. However, she was not interested in her surroundings, could not stand even with support and could not talk. Feeding was difficult and mainly from the bottle and she was very constipated (Fig. 1).

A radiograph (Fig. 2) showed retarded ossification of the skull bones. The anterior and posterior fontanelles remained open. Several Wormian bones were present and the bones at the base of the skull were thickened and the base was short. A radiograph of the lower limbs (Fig. 3) showed retarded ossification of all the epiphyseal centres with sclerotic lines at the ends of the long bones. The ossification centres showed epiphyseal dysgenesis. A radiograph of the wrist also showed delay in ossification and dense lines at the lower ends of the radial and ulnar shafts. Radiographs of abdomen and hips

FIG. 1.—Photograph taken one week after beginning thyroid treatment.

(Fig. 4) showed extensive calcinosis in both renal areas and delay in ossification of the femoral heads. A radiograph of the spine (Fig. 5) showed that maturation of the vertebrae was retarded and that there was deformity of some vertebral bodies. An intramuscular pyelogram showed impaired renal function. A radiograph of the chest and an electrocardiograph were within normal limits.

A blood count gave haemoglobin 60%, red cells 2,660,000 per c.mm., white cells 14,200 per c.mm. (81% neutrophils, 19% lymphocytes). The blood cholesterol

FIG. 2.—Radiograph of the skull, showing open anterior and posterior fontanelles: short base with thickened bones.

level was 458 mg. %, serum alkaline phosphatase 16·5 units, serum inorganic phosphates 6·6 mg. %, serum calcium 12·2 mg. %, serum calcium ions 6·1 mg. per 100 ml., blood urea 148 mg. %. The serum proteins were 5·8 g. % and the CO_2-combining power of the blood was 46 vol. %.

A trace of protein was found in the urine, numerous pus cells, and an occasional red blood cell and granular cast. The *p*H was 5·0 and the CO_2-combining power was 0 vol. %. Chromatography of the urine showed no abnormal amino-aciduria; glycine, alamine and cystine were detectable in small amounts.

Treatment was begun on February 12 with thyroid, grain ¼ daily, increased to grain 1 daily on March 6, and to grain 1½ daily on March 29, in divided doses. Frequent enemas were necessary.

While in hospital the child's progress was rather disappointing. Her general appearance improved. The skin became smoother, the tongue smaller and the abdomen less protuberant. The extremities became pink and warm. The blood cholesterol level fell from 458 to 265 mg. %. There was, however, no change in

FIG. 3.—Radiograph of the lower limbs, showing retardation of ossification, sclerotic lines at the ends of long bones, and epiphyseal dysgenesis of ossification centres.

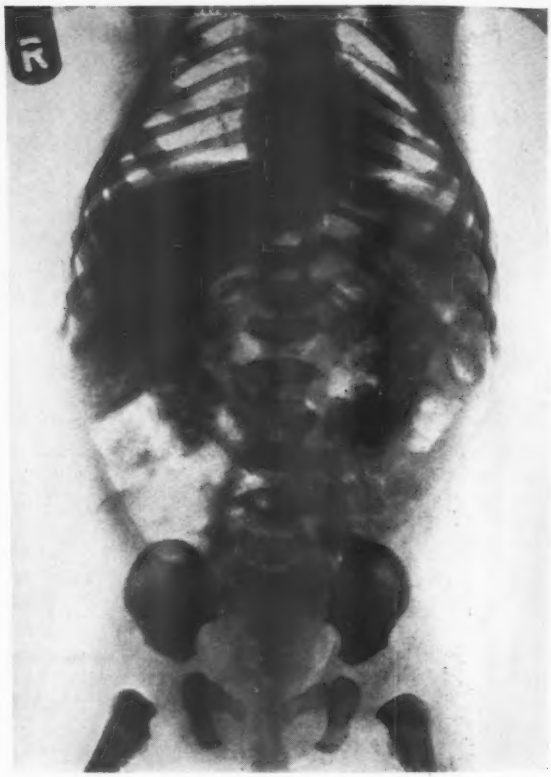

FIG. 4.—Radiograph of the abdomen and hips, showing nephrocalcinosis and delay in ossification of femoral heads.

her feeding, and she continued to behave like a 6-month-old baby in this respect; she seemed drowsier at times and was not smiling so much. On admission she could just support herself in the sitting position, but gradually she was unable to do this. She remained constipated and lost a little weight. We thought that this regression was in part due to being in hospital and lack of maternal care and so she was discharged on March 29.

When seen on July 7 (after five months of thyroid therapy) there was a striking improvement (Fig. 6). A considerable amount of new soft hair had grown in and the skin was smooth and had lost its grey, mottled appearance. The child was warm and the extremities were pink. The tongue was small and 15 teeth had

erupted. She had lost the thickened subcutaneous tissues. She was taller, had lost 2 lb. in weight and her infantile proportions. The abdomen was no longer protuberant, the girth being 15 in. The skull circumference remained the same, but the fontanelles were smaller. For about a fortnight she had been attempting to pull herself into the sitting position; she could now sit for a few minutes without support, and had more balance. Her mother

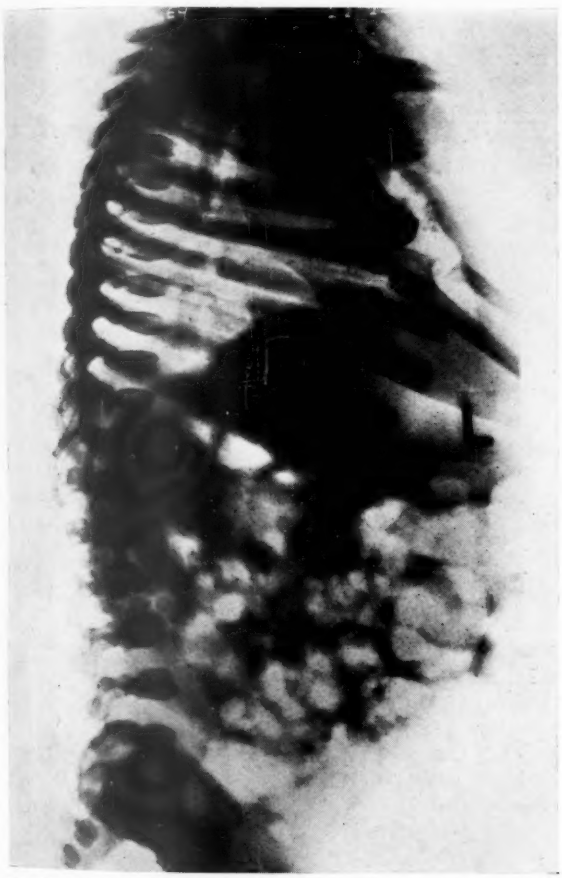

FIG. 5.—Radiograph of the spine, showing deformity of the vertebral bodies.

thought that she was taking more notice and she preferred a cup to a bottle. She was having a daily bowel action without aperients and the only trouble seemed to be that she was a little cross at nights; in view of this the thyroid was not increased from 1½ grains daily.

The radiograph taken on July 7 showed that the anterior and posterior fontanelles were smaller, but otherwise there was no change. No centres of ossification had appeared in the wrist.

On August 14 the blood urea was 114 mg. %, serum protein 6·55 g. %, serum calcium 15·1 mg. %, serum calcium ions 7·2 mg. %, serum phosphate 7·0 mg. %, serum alkaline phosphatase 19 units %, and blood cholesterol 195 mg. %.

Discussion

Wilkins (1950) emphasizes that a diagnosis of hypothyroidism should be made on '(1) physiologic evidences of thyroid deficiency—sluggishness, impaired circulation and constipation, and (2) evidences of retarded growth and development—delayed bone age and dental development, infantile facies and

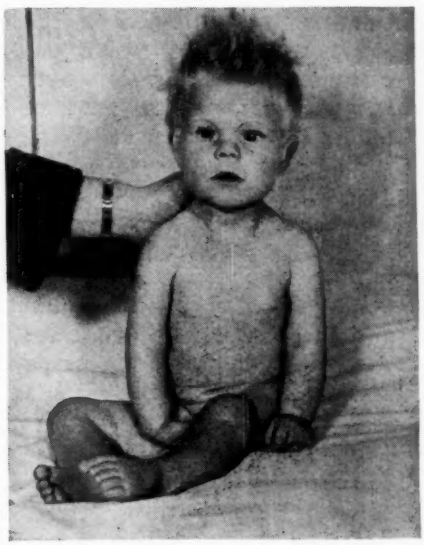

FIG. 6.—Photograph after five months of thyroid treatment.

skeletal proportions and epiphyseal dysgenesis'. All this evidence is present in the case described, which is an extreme example of untreated hypothyroidism. The serum phosphatase estimation, which is a useful confirmatory test of hypothyroidism, was not reduced as is almost constantly so in this endocrine disorder (Gaisford, 1952). The interesting feature in the case is the extensive nephrocalcinosis and the raised level of blood serum calcium.

Aub, Bauer, Ropes and Heath (1927) found that in hypothyroidism calcium and phosphorus are deposited in greater concentration in the bones and eliminated less freely in the urine and stools than they are in the normal person. Robertson (1941) studied the calcium and phosphorus balance in three cases of myxoedema in adults and found that the blood serum level of calcium and phosphorus was normal but the output greatly reduced. Braid (1951) reports a case in which there was clinical evidence of calcium retention in that there was increased density of the bones and a diffuse calcinosis of the soft tissues. This occurred in a child of 2¼ years who was a case of untreated hypothyroidism. This child, however, had a normal blood calcium in

contrast to the case described here where the blood calcium level was raised.

Conditions causing hypercalcaemia have been reviewed by Wilkins (1950). They include vitamin D poisoning, osteoporosis of disuse, hyperparathyroidism, neoplasms and sarcoid. There was no evidence in this case that excessive doses of vitamin D had been given. In vitamin-D intoxication, renal impairment with extensive deposition of calcium in the inter-tubular tissues of the kidney can occur. Nephrocalcinosis has been described in osteoporosis of disuse. In this condition hypercalcaemia may occur, but the serum phosphorus level is usually normal and the phosphatase not increased, in contrast to the case described here, where both the serum phosphorus and phosphatase were raised. This child was immobile, because of mental retardation, for four and a half years, and might well fit into this group. There was no evidence of demineralization of bones as occurs in hyperparathyroidism, but in this condition there may be metastatic calcification including deposits of calcium in the kidneys and urinary tract.

Lightwood (1952) describes cases of idiopathic hypercalcaemia, which clinically are indistinguishable from renal acidosis. Two of his series of 10 showed nephrocalcinosis. The blood chemistry showed a raised blood calcium and urea without concurrent renal acidosis. Payne (1952) describes the blood chemistry in idiopathic hypercalcaemia. There was a raised plasma protein as well as raised blood calcium and urea. The phosphate, phosphatase, chloride and bicarbonate levels were normal. The renal function was depressed in the active phase.

The prognosis is poor in regard to mental development and duration of life; first because of the age at which treatment was begun and secondly because of the poor renal function and raised blood urea. All that can be hoped for is an improvement in the physical condition, which has already taken place. There is a danger in treating this type of case (where thyroid therapy has been withheld until after the most active period of growth of brain and body) of producing a manic type of psychosis and so it is wiser to under-treat and leave the child placid and manageable (Wilkins, 1950).

Summary

A case of hypothyroidism with associated nephrocalcinosis is described. The possible aetiology of the renal calcification and the prognosis are discussed.

I should like to thank Dr. K. R. Llewellin for his help in the preparation of this paper and for permission to publish the case.

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METASTATIC TUBERCULOUS ABSCESSES

BY

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In the past three years we have studied several children suffering from chronic tuberculous ulceration of the skin. These ulcers, usually multiple, were formed by the rupture through the skin of a tuberculous abscess which began beneath it. The ulcer slowly healed leaving a depressed scar.

There are brief references to this type of ulceration in both paediatric and dermatological textbooks, but we cannot find a clinical description of the lesion clearly differentiating it from an abscess arising from tuberculous lymphadenitis or from a focus in bone, or from tuberculosis cutis; nor can we find any reference to the relation of the lesions to the time of primary infection.

We think, therefore, that it will be useful to describe the course of these uncommon lesions and demonstrate their relation to the primary infection.

Four cases are recorded. We have seen three others, but our notes are insufficient to include them. The seven cases occurred in approximately 1,000 children suffering from tuberculosis seen in the hospitals and various clinics in the city. The incidence, therefore, cannot be more than 1% of tuberculous children and probably is much less.

Case Reports

Case 1. M.R., a girl of 8 years, one of a family of six children living on Tyneside, was brought to hospital in July, 1951. About nine months earlier her mother found a small painless lump under the child's left buttock. During the next six months the lump turned blue slowly and eventually discharged blood-stained fluid. Three months afterwards a similar lump was seen on the right thigh, and within the next two months two others, one on the left buttock and one in the right popliteal fossa. This last lesion discharged following a kick.

The lumps were never painful. They were first under the skin and separate from it, but later became attached as they broke slowly through to discharge. Her general health remained good and she was sent to hospital because the resulting ulcers were not healing.

One of her elder sisters had been in a sanatorium three years earlier suffering from a tuberculous pleural effusion and a lung lesion, and there were two other young adults with pulmonary tuberculosis living near.

On examination, she was a sturdy child with two open ulcers, one on the right buttock and one behind the left knee; the scar of one other on the left buttock and a small unruptured abscess above this (Fig. 1). The ulcers were roughly circular with narrow, blue-red margins fading into the skin; the edges were undermined and the floors were of reddish granulations covered with thick yellow pus. The abscess which had not opened was painless, hard, fixed to the skin but free over the deeper tissues. The overlying skin was bluish-red with some superficial desquamation.

The tuberculin skin reaction was positive; the Wasser-

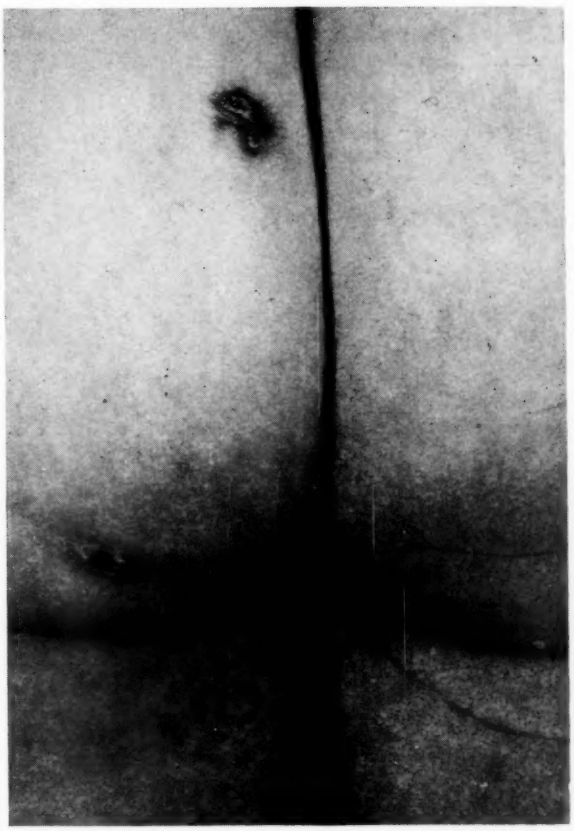

FIG. 1.—Case 1: left buttock, showing an ulcer scar and an unruptured abscess above.

mann and Kahn tests were negative. A radiograph of the lungs showed a small right pleural effusion with a segmental opacity, of the type commonly seen in primary tuberculosis, in the upper lobe. Two of the ulcers were examined histologically. The reports (Dr. J. Hart Mercer) stated:

> 'Tubercle follicles are demonstrable at the margins of the otherwise non-specific granulation tissue lining the base of the dermal ulcer . . . This ulcer, too, shows unmistakable tuberculosis.'

She received no specific treatment but was transferred to a children's sanatorium. There, the local lesions healed in a few weeks; the radiological shadows in the chest cleared more slowly. In April, 1952, she went home and has remained well since: no further skin lesions have developed; recent radiographs show faint calcification in the right paratracheal glands.

This child developed multiple abscesses in the early post-primary stage, probably within 12 months of infection.

Case 2. C.W., a girl, aged 12 years, was admitted to hospital in November, 1949, with fever, abdominal pain and tenderness. Her tuberculin reaction was strongly positive and a radiograph of the chest was normal. The pain settled in a few days and she was allowed home with a provisional diagnosis of primary abdominal tuberculosis. Remaining well for four months, she was then readmitted in a further attack of abdominal pain and found to have a left-sided pleural effusion. She was transferred to a children's sanatorium where she stayed until March, 1951, 16 months after the initial illness. During this time she had right-sided chest pain followed by a pleural effusion. This cleared without complication and on discharge she was well.

FIG. 2.—Case 2: the ulcer on the back of the left ankle.

Some 14 months later, and two and a half years after the primary infection, while staying in another part of the country, she developed a tender, fluctuant swelling over the upper part of the right tibia and was sent to an orthopaedic hospital. No details of her treatment are available but she had a plaster splint applied and returned to her home in Newcastle a few days later, where she was again seen at hospital. Radiographs of the knee showed no bony abnormality, and she was watched as an outpatient for three months. During this time she developed an ulcer over the left tendo achillis, and on questioning admitted that a lump had been there for some four months (Fig. 2). The abscess at the upper end of the right tibia had remained and she was also found to have a discharging 'sore' over the metatarso-phalangeal joint of the second left toe.

The Wassermann reaction was negative. Radiographs of the knee and ankle again showed no bony abnormality. Pus aspirated from the abscess over the right tibia was sterile.

She was then readmitted to hospital, the abscess on the tibia was excised, and a section taken from the ulcer on the left ankle. The pathological report (Dr. R. Paterson-Smith) stated that histological examination of both tissues showed fibro-caseous tuberculosis, the former a cyst filled with caseous material and the latter an ulcer with tuberculous granulation tissue and caseation.

Following three months' treatment with streptomycin and P.A.S. the operation site and the ulcers were all soundly healed. Radiographs were still normal and she was discharged. She is now working away from Newcastle but is reported to be well.

In this case the abscesses started at least two and a half years after the primary infection and all three lesions appeared within six months.

Case 3. N.L., a girl, aged 7½ years, was first seen in 1950 complaining of abdominal pain. The tuberculin reaction was probably positive at that time but the records are not completely clear on this point.

She returned two and a half years later having been well until three months previously when she had a severe attack of scarlet fever. Within two weeks of her discharge from the fever hospital she noticed a small lump in the front of the right thigh just below the groin. This turned red and after about two more weeks discharged blood-stained pus. A similar but larger lump then developed on the outer side of the left knee and became fluctuant. Neither lesion was painful. She had been given penicillin by her family doctor, and when this had no effect was referred to hospital (Figs. 3 and 4).

Her tuberculin reaction was positive; sterile pus was aspirated from the lump at the knee. Following aspiration the abscess leaked and tubercle bacilli were cultured from the pus. Biopsy of the skin showed active tuberculosis. Radiographs of the chest and abdomen

FIG. 3.

FIG. 3.—Case 3: the ulcer on the right thigh.

FIG. 4.—Case 3: the ulcer over the head of the left fibula.

FIG. 5.—Case 3: the right thigh ulcer healed—three months later.

FIG. 6.—Case 3: the ulcer at the left knee, showing breakdown and formation of the secondary ulcer.

FIG. 4.

FIG. 5.

FIG. 6.

showed no calcification but there was a tuberculous focus in the transverse process of the right eleventh rib. There was no evidence of bone disease in the right femur or left tibia or fibula.

She was given a short course of streptomycin. The thigh lesion healed after scabbing over (Fig. 5). The skin over the abscess at the knee broke down, forming two ulcers separated by a bridge of unhealthy skin. For two or three weeks the base remained covered with a dirty slough, but this cleared slowly, leaving a granulating base (Fig. 6). This ulcer took several months to heal, but a year later there was a firm depressed scar, the rib lesion had disappeared, and the girl was well (Fig. 7).

The lesion in this case became manifest about two years after the primary infection following a streptococcal sore throat. We do not know if the spread occurred then or if, at a time of reduced resistance, the abscesses developed from bacilli previously deposited.

Case 4. M.N., a boy, aged 10 years, was seen in February, 1954, with a fluctuant swelling at the lateral border of the right pectoralis major. Twelve days previously he had fallen off a sledge and the next day noticed a lump. Probably the fall had only drawn his attention to it for there was no bruising; the lump was painless and fluctuant, about 2 in. in length. There was no gland swelling nor any skin lesion (Fig. 8).

The boy was not ill and we could not find any clinical or radiological evidence of primary infection or underlying bone infection, though his tuberculin reaction was positive. Pus aspirated from the abscess grew tubercle bacilli. During the next few days the lump increased in size, spreading under the pectoralis major so that pressure on the muscle produced a distinct bulge. The skin was becoming discoloured and therefore the abscess was drained. With streptomycin and isoniazid therapy the wound healed by first intention. The boy has remained well.

FIG. 8.—Case 4: the abscess presenting at the lateral border of the pectoralis major.

FIG. 7.—Case 3: the scar over the head of the fibula 12 months later.

This boy had a single deep abscess and as yet has no clinical or radiological signs to locate the site of the primary lesion. This suggests that the infection is recent and we may later find calcification appearing in the neck, chest or abdomen.

Discussion

In each of these cases the history is of an abscess or abscesses forming in the subcutaneous tissue and slowly involving the overlying skin. All except the last have discharged blood-stained pus and left indolent ulcers which have taken some weeks or months to heal. With one exception (not seen by us at that stage) these abscesses were painless. They were unrelated to trauma or skin wound. In two, and probably in a third, primary tuberculous infection was already known to have taken place, and the fourth was proven to be tuberculous although the site and time of the primary infection are not yet known.

All these facts can be fitted to the natural history of primary tuberculosis by assuming that in each

case the abscess had its origin in haematogenous spread from a primary infection; in Cases 1 and 4 during the first year after infection and in Cases 2 and 3 in the third year afterwards.

None of the children had clinical miliary tuberculosis, although in three of the four cases there were multiple foci present—either before the abscesses appeared or at the same time. Two children had a pleural effusion and one a tuberculous rib. In none of the cases was there enlargement or caseation of the regional lymphatic glands draining the site of the abscess or involvement of underlying bone.

These cases are clinically similar to tuberculous abscesses occurring after intramuscular or subcutaneous injections, whether they arise from the deposition of bacilli during the stage of bacillaemia at the site of tissue damage or are introduced by the injection, providing in each case that the subject has already undergone primary infection (Ebrill and Elek, 1946; Hounslow, 1946; Forbes and St. Clair Strange, 1949). An identical abscess has been seen after auto-inoculation of living tubercle bacilli (Chien and Wiggins, 1954). In tuberculin-negative persons injection of tubercle bacilli causes a primary tuberculous abscess with involvement and caseation of the regional glands.

The common types of tuberculous abscess resemble those described above, but are easily distinguishable. Caseating glands from a primary complex may form a cold abscess, but the underlying gland mass will always be found if sought. The origin of a tuberculous abscess arising from an infected bone or joint can be demonstrated by radiography of the affected part.

Summary

Four cases of metastatic tuberculous abscess in children are described, and their place in the natural history of tuberculosis discussed. They are presumed to be haematogenous spread from a primary infection occurring during a period of bacillaemia or of lowered resistance.

We would like to thank Dr. G. A. Neligan for referring Case 1 and Mr. Michael James who allowed us to see Case 2 when she was admitted to hospital; Dr. C. A. Green for the bacteriological reports; and Mr. J. D. Duncan, Director of the Department of Photography, for the photographs.

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BILE PERITONITIS IN INFANCY

BY

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Extravasation of bile into the peritoneal cavity of infants and children, unassociated with trauma, has been described sufficiently rarely in the past to merit the reporting of two further cases. The term 'bile peritonitis' is misleading as a description of the clinical picture seen in these particular infants. The condition is essentially an escape of bile following rupture of some component of the extra-hepatic biliary system, forming a collection in the peritoneal cavity. Some of this is fluid drawn from the various peritoneal and intestinal tissues by the relatively high osmotic pressure of the escaping bile (Gross, 1953), but there is no acute peritonitis. This is, therefore, a bile ascites unaccompanied by disease of the liver or peritoneum.

Case Reports

Case 1. This child, the second of healthy parents, was admitted to hospital at the age of 6 weeks in December, 1949. He had been born normally, weighing 8 lb., after an uneventful pregnancy. The history was that his stools had been white since the passage of meconium ceased, that he had been jaundiced since the age of 2½ weeks, and that the intensity of the jaundice had not increased; two to three days before admission his abdomen had become distended, and bilateral inguinal herniae had appeared. On admission he was afebrile, slightly jaundiced, but not acutely ill; generalized wasting emphasized his gross abdominal distension and large herniae. He had in addition bilateral talipes equinovarus. The stools were cream coloured, but the urine contained neither bilirubin nor excess of urobilin. Both mother and child were Rh positive, and had negative Wassermann reactions. The abdominal distension increased slightly after admission and caused the infant some respiratory embarrassment. Paracentesis abdominis gave 50 ml. of heavily bile-stained fluid, sterile on culture, and in view of this laparotomy was performed. At operation, a large amount of bile-stained fluid was found in the peritoneal cavity. The gall bladder, cystic and hepatic ducts looked normal, as did the liver. The common bile duct was explored and a probe passed down into the duodenum. Some resistance was met at the sphincter of Oddi, but there was no genuine obstruction. A drain was left down to the duct and the abdomen closed, bile continuing to drain for some days. On the fifth post-operative day the child passed his first normal stools. The tube was removed on the ninth post-operative day, by which time the jaundice had disappeared. He has made good progress, and has been symptom free since.

Case 2. The first child of healthy parents, this boy was born naturally at term after a normal pregnancy and labour, weighing 7 lb. 7¼ oz. His mother thought that he had been slightly jaundiced from birth, and on leaving the maternity home she found he was passing white stools and dark urine. At the age of 1 month he developed a large left scrotal hernia, followed a week later by an equally large right-sided hernia. His progress otherwise was considered satisfactory, feeds were taken well, and he gained weight normally.

When first seen at the age of 8 weeks in March, 1952, he was an active, alert baby, not ill, weighing just over 10 lb. Apart from slight jaundice, the most striking features clinically were the large herniae, and a distended abdomen. Shifting dullness could be demonstrated, and the liver felt two fingerbreadths below the costal margin. The urine contained some bilirubin, but no urobilinogen, the faeces neither bilirubin nor stercobilin. The plasma bilirubin (5·4 mg.) and alkaline phosphatase (83 units) levels were raised. Both mother and child were Rh positive and had negative Wassermann reactions.

The similarity of this case to the first led to a diagnostic paracentesis abdominis on the day following admission, and a small amount of heavily bile-stained fluid was withdrawn, sterile on culture. An increasing abdominal circumference causing him some respiratory distress led to three more taps over the next eight days, 25 oz. of fluid being withdrawn in all. Fluid continued to accumulate, however, and as the infant's condition was deteriorating slightly, the decision to investigate further was made, and laparotomy performed three weeks after admission. On opening the peritoneal cavity, a further 12 oz. of bile-stained fluid was drained. There were many adhesions round the gall bladder area, and a small perforation was seen in the common bile duct just above the duodenum, beside which was lying a greenish black stone, 3 mm. in diameter. Probing showed that only the upper part of the common duct was patent, and that the lower part below the perforation was not. The opening in the common bile duct was enlarged slightly and was anastomosed to the duodenum over a short length of rubber tubing. The peritoneal cavity was drained by a tube to the region of the anastomosis. Culture of the bile was again sterile. Forty-eight hours after operation, the infant passed his first normal

yellow stool. Four days after operation the drain was removed, the wound was well healed after 10 days, and he started to gain weight satisfactorily. The child was discharged from hospital a few days later, jaundice having disappeared completely, the stools remaining normal in colour and consistency. Two months later liver function tests were as follows: Plasma bilirubin 0·2 mg. %, alkaline phosphatase 23 units, total proteins 6·2 g. % (albumin 4 g. %), and flocculation tests (thymol turbidity and colloidal gold) negative. The small rubber tube was passed via the bowel some three months after the operation. The baby has remained well and symptom free since, making excellent progress, and a recent repeat of the liver function tests has shown normal results.

Discussion

Caulfield (1936), stating that severe trauma had been responsible for any previously reported cases that he could find, put on record the first two cases with a different aetiology. These were both full-term male infants, born after normal deliveries, and the first symptoms in each case were noted at the age of 3 weeks. The first infant, in whom slight jaundice and the passage of white stools were quickly followed by increasing abdominal distension and scrotal swelling, was subjected to laparotomy at the age of 6 weeks, as paracentesis producing heavily bile-stained fluid had been followed by fairly rapid accumulation with some respiratory distress. At operation it was found impossible to distinguish the anatomy of the extra-hepatic ducts, and simple drainage to this region was carried out, with complete recovery. The second infant did not develop abdominal and scrotal swelling or jaundice until three weeks after the appearance of white stools. He was not operated on, and died at 11 weeks. Necropsy showed stenosis of the common bile duct, rupture of the duct just above the stenosis, and a large bile-filled sac in the upper abdomen which had ruptured and filled the peritoneal cavity. Death was presumed to be due to inanition.

Hindmarsh (1947) described the case of a 22-month-old girl, previously healthy, who had presented after a 36-hour illness with abdominal distension, generalized abdominal tenderness, fever and shock. She was found at operation to have a large quantity of bile-stained fluid in the abdomen. Simple drainage was performed, and she made a good recovery. The bile was sterile on culture. A cholecystogram done several months later was normal.

Byrne and Bottomley (1953) reported a fourth case, that of a 3-week-old girl, thriving until she presented with a 36-hour illness, showing abdominal distension, generalized abdominal tenderness, fever and shock. She was found at operation to have a large quantity of bile-stained fluid in the abdomen, a completely solid gall bladder embedded in the right lobe of the liver, and several small cystic masses at the junction of the cystic and common ducts, one of which was ruptured and presumably the site of extravasation. Simple drainage again gave a complete recovery, though follow-up is being continued.

The combination of stools without bile pigment, indicating a complete obstruction to the flow of bile, with slight jaundice and slight or absent bilirubinuria, suggests that providing it is being normally formed, the bilirubin is not being reabsorbed into the blood stream but is escaping elsewhere. The presence of abdominal distension and shifting dullness in the two cases now recorded, with these other findings, thus made the diagnosis almost certain. It is interesting to note that in both of Caulfield's cases, as in ours, the rise in intra-abdominal pressure was sufficient to cause bilateral inguinal herniae, and it is a reflection on the mildness of the illness that in three of the four cases it was the presence of the herniae alone that worried the parents sufficiently to seek medical advice. Diagnosis in Hindmarsh's and Byrne's cases, on the other hand, was impossible pre-operatively, and the histories of both conform much more to the picture seen in adults, when extravasation of bile presents as an acute abdominal emergency with considerable associated shock. The reason for these two contrasting modes of presentation is obscure. A gradual leakage of bile over a longer period as opposed to a sudden large extravasation may be the answer, but it is at least possible that the formation of large scrotal herniae as intra-abdominal pressure rose in the four male infants acted as a kind of safety valve, thereby altering the clinical picture.

The aetiology of Case 1 is uncertain. At operation, apart from slight resistance to the probe at the sphincter of Oddi, the extra-hepatic biliary system appeared normal in all respects, and the actual site of rupture was not found. A tempting theory is that the probing bougie dislodged a plug of inspissated bile, possibly at the site of resistance, so releasing the obstruction. The infant had a leucocytosis (as did the cases of Hindmarsh and Byrne), but he was afebrile, the bile-containing ascitic fluid was sterile on culture, and it is difficult to correlate the rather insidious history with an acute infection. In Case 2 a definite abnormality, stenosis or failure of development of the lower end of the common bile duct, was present, with the actual perforation visible above it. The minute gall stone found may have been instrumental in causing the rupture, though it may equally well have been formed

after the extravasation had occurred. A similar anomaly, also with rupture above the stenosis, was responsible for Caulfield's second case, and rupture of a congenital cyst in the region of the cystic duct gave rise to symptoms in Byrne's and Bottomley's case. Caulfield's first case is more difficult to explain: perhaps again a plug of bile, or even a gall stone could be postulated, but proof of the former anyway would be impossible and it must remain an academic point. Hindmarsh's patient is also puzzling, and one wonders if, in view of her age, she could, without her parents' knowledge, have sustained some trauma before the onset of symptoms.

This condition, as Caulfield stressed, is an indication for surgical exploration, though it is probably justifiable to try the effect of paracentesis one or more times first. Neither of the infants now described presented as abdominal emergencies, which meant that adequate preparation for operation, including the administration of vitamin K, could be undertaken. Simple drainage after probing the extrahepatic ducts in the first case, and anastomosis of the common duct above the stenosis to the duodenum in the second, were successful. Simple drainage alone proved successful in the three other surviving cases previously reported.

The prognosis of this condition in infancy and childhood when surgically treated appears to be good. Perhaps the very fact that the bile is released means that back pressure on the liver and therefore subsequent damage to it is avoided.

Summary

Two cases of so-called bile peritonitis in infancy, unassociated with trauma are reported, and the available literature described.

The diagnosis and aetiology and treatment are discussed.

It is stressed that the condition is an indication for surgical treatment.

Both these children were admitted under the care of Dr. Smallpeice, and we should like to thank her for permission to describe the cases, and for much encouragement and help in the preparation of this article.

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SUPERFICIAL GANGRENE OF THE SKIN IN CHICKENPOX

BY

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Gangrene of the skin is a very rare complication of chickenpox. Barenberg and Lewis (1927) saw one example in over 2,000 children and Wishik and Bullowa (1935) saw four examples in 2,534 children with chickenpox. The condition was probably first described by Stokes (1807), but was first discussed in some detail by Jonathan Hutchinson in 1882. The latter's paper is notable for the beautiful reproduction in colour of a painting of a child with multiple areas of gangrene. Hutchinson termed the condition 'varicella gangrenosa'. Crocker (1903) described it under the heading 'dermatitis gangraenosa infantum (synonyms varicella gangraenosa, pemphigus gangraenosa, rupia escharotica, echthyma térébrant, echthyma gangrenosum)'.

In most of the cases described the gangrene occurred around one or more of the chickenpox lesions (Hutchinson, 1882; Crocker, 1903; Barenberg and Lewis, 1927; Rundle, 1929; Apert and Goldberg, 1930; Lavergne, Helluy and Bolikowska, 1938; Joe, 1947). In the majority of cases described the lesions were multiple, but in both Storrie's cases (1914) there was a single gangrenous area. In almost all the cases described the gangrene developed between the fourth and seventh day of the eruption.

Views as to the aetiology of the condition are varied. Hutchinson (1882) held that it was due to an individual susceptibility to varicella, a view with which Barenberg and Lewis (1927) and Stoesser and Lockwood (1938) agreed. Schamberg and Kolmer (1928) regarded the condition as non-specific, stating that similar manifestations may occur in vaccinia, variola, scarlatina and various dermatoses.

Several workers, for example, Schamberg and Kolmer (1928), Rundle (1929) and Joe (1947), thought that it occurred largely in weakly and malnourished children, many of them with tuberculosis, though other workers were impressed by the good general condition of affected children, for example, Dykes (1927) and Barenberg and Lewis (1927).

Several workers ascribed the complication to secondary infection. Krjukoff (1899), Goodall (1928) and Joe (1928) described cases from which the Klebs-Loeffler bacillus was isolated. Banks and McCartney (1937) isolated the haemolytic streptococcus of Griffith Type 23 from lesions in their case, and ascribed the infection to an associated tonsillitis from which the same organism was recovered. Storrie (1914) obtained *Staphylococcus pyogenes* from his two cases. Nichols (1934) isolated the same organism from a case with superficial gangrene of the abdominal wall following infection of a vesicle. Gillespie and Porter (1952) described the occurrence of cellulitis or gangrene in three members of one family—the mother and two children: the lesions had to be incised and drained. In three of the cases described by Wishik and Bullowa (1935) the gangrene was preceded by cellulitis and high fever.

In some cases there was an associated thrombocytopenic purpura (Stoesser and Lockwood, 1938); Batch and Sepkowitz, 1952). In most of the studies in the literature there is no record of a platelet count. Watson (1934) commented on the ecchymosis surrounding the gangrenous area in his case.

Almost all writers emphasized the grave toxaemia experienced by their patients (Hutchinson, 1882; Storrie, 1914; Barenberg and Lewis, 1927; Dykes, 1927; Gordon, 1927; Goodall, 1928; Nichols, 1934; Watson, 1934; Banks and McCartney, 1937). Most of the patients described by the above writers died. Storrie collected 43 cases from the literature, 29 of which died. On the other hand one of the patients described by Wishik and Bullowa (1935) was never ill, though he developed gangrene of all the fingers of one hand, the dorsum of one foot, and part of both legs. New areas of gangrene developed 16 days after the first. Schamberg and Kolmer (1928) described the occurrence of mild cases. Dykes (1927), Watson (1934), Wishik and Bullowa (1935) and others noted the mildness of the initial chickenpox. The patient described by Dykes, for instance, had no more than 20 vesicles in all.

Several workers commented on the rapidity with which the gangrene spread. In the case described by Watson (1934), for instance, a small discoloured area developed on the fourth day of the chickenpox eruption, gangrene was obvious eight hours later, and 20 hours later there was a gangrenous area 6 in. wide spreading from the axilla to the iliac crest. The patient recovered. The patient described by Banks and McCartney (1937) died within 48 hours of the appearance of gangrene.

Below is a description of a child observed by us in the Children's Hospital at Sheffield.

Case Report

The patient was a well nourished 3-year-old girl who developed typical mild chickenpox a week after her brother started with it. In the evening of the seventh day of the eruption she went to bed well, but woke on the following morning with a swollen and tender purple patch, about 1½ in. in diameter, with red edges, on the front of the left side of the chest. She was not at all poorly. An hour later the patch was said to be almost twice its initial size. There had been no injury and no ointment or other medication had been applied to the area. On the following day she was brought (walking) into the Out-patient Department.

On examination she was a well looking girl, weighing 30 lb., and with a normal temperature. Her blood pressure was 85/60 mm. Hg. There was a typical rash of mild chickenpox. On the front of the left side of the chest there was an irregular ovoid patch of gangrene, measuring 8 × 4 cm., with a clearly demarcated red periphery about 1 cm. in width (Figs. 1 and 2). The whole area was somewhat indurated and raised above the level of the surrounding tissues, but there was no suggestion of cellulitis. The temperature of the gangrenous patch was less than that of the tissues around. On pressing the stethoscope bell into the surrounding tissues there was a fine crepitus, similar to that obtained in the presence of subcutaneous emphysema. The skin surface was not bruised or excoriated. There was only slight tenderness to the touch. There was no associated lymphadenopathy, and there were no other abnormal physical signs elsewhere in the body. There was no evidence of arteriosclerosis. Instructions were given that the affected area should be kept dry and absolutely clean, but no specific therapy was prescribed.

Special investigations were negative. The blood count was as follows: Haemoglobin, 11·7 g. %; red cells 3,300,000 per c.mm.; white cells 13,500 per c.mm. (neutrophils 59%, lymphocytes 30%, monocytes 7%, eosinophils 4%); platelets 433,000 per c.mm.

The bleeding time was 3½ minutes. The Mantoux test (1 in 1,000) was negative. The urine was normal chemically and microscopically. A radiograph of soft tissues underlying the gangrenous area did not help. The gangrenous area being quite dry and clean, no bacteriological examination was possible.

She made an uneventful recovery. She remained well and afebrile, with no toxaemia. At no time was there any serous or other discharge from the area. On the day after admission the swelling was less marked, and there was no crepitus on pressure. There was some surrounding discoloration, as if there were an underlying haematoma, but an aspirating needle was passed through adjacent normal skin and under the lesion, without revealing any sign of blood. On the ninth day after admission desquamation began in the peripheral red area, revealing an underlying healthy pink skin. She was discharged home after 15 days in hospital. The gangrenous area gradually shrank, so that by the 22nd day it measured 7·7 × 2 cm. Six weeks after the onset desquamation of the gangrenous area began, leaving a clean healed scar underneath. Eight months after the onset the affected area had healed completely (Fig. 3), leaving a scar

FIG. 1.—On the day after admission.

FIG. 2.—On the day after admission (close-up view).

FIG. 3.—Eight months after the onset.

measuring 6×2 cm., some of it soft, some of it a little indurated. It was felt that for the present no plastic surgery on the scar was advisable because it was hoped that it would contract down still more. The girl was asked to return in a year for review.

Comment

The outstanding feature of our case was the absence of fever or toxaemia in spite of a fairly large patch of gangrene. There was no sign of secondary infection and the patch of gangrene bore no obvious relationship to any chickenpox lesion: it did not surround or abut on a vesicle or scab. The platelet count was normal. The above facts lend some support to the original view expressed by Hutchinson (1882) that gangrene in these cases may represent an individual susceptibility to varicella. Other cases are clearly due to secondary infection.

Summary

A case of superficial gangrene of the skin in a mild case of chickenpox is described. There was no evidence of secondary infection. The child at no stage showed toxaemia or an elevation of temperature, remaining well throughout. The treatment was entirely conservative.

We wish to thank Dr. Doris Fletcher, dermatologist, for seeing this case. Dr. Judith Hay kept accurate day-to-day records of the size and appearance of the lesion. The clinical photographs are by the Department of Medical Photography in the United Sheffield Hospitals. We also wish to thank the family doctor, Dr. J. C. Cooper of Sheffield, for referring the girl to us.

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SUBACUTE AND CHRONIC INTUSSUSCEPTION IN INFANTS AND CHILDREN

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 9, 1954)

Most writers on the subject claim that chronic intussusception is rare in childhood. Thus Still (1921) stated that in children it occurs 'rarely indeed'; Monrad (1927) wrote: 'Chronic invaginations in my experience are extremely rare in small children'; Beaven (1929) noted that 'judging from the number of cases reported, chronic intussusception is an extremely rare disease in children'; and Nyborg (1943) stated that the condition 'is very rare in young children'. We have recently encountered two cases in infants within a short period and, as a result of our scrutiny of hospital records and of the literature, we do not think that this emphasis on rarity is justified.

Case Reports

Case 1. A boy of 5 months was admitted to the Duchess of York Hospital for Babies, Manchester, in May, 1954. He was the firstborn of healthy young parents and he had progressed satisfactorily until four weeks before admission. At that time he began to get attacks of 'colic', in which he screamed, drew up his legs and went pale. These episodes were brief—a few minutes only—and between attacks he seemed quite well. For several days he had two or three such attacks each day without other symptoms. Thereafter he began to vomit and about the same time he developed what his mother described as 'black diarrhoea'. The diarrhoea and vomiting persisted as did the screaming attacks until he came into hospital. For a week or two before admission he was chesty and he became progressively more miserable and lost weight steadily. Several days before admission he had begun to refuse his feeds. Examination in the out-patient department showed a pale, alert infant who had recently lost weight. Apart from some redness of the throat nothing abnormal was discovered. When he was re-examined in the ward an hour or two later two masses were felt in the abdomen, one in the right flank and the other under the left costal margin. It was at first thought that these were the kidneys. No abnormalities were found in the urine and the blood urea was normal. In the first 24 hours in hospital the infant vomited several of his feeds and passed a dark, frothy stool which gave a positive benzidine reaction. Repeated examination of the abdomen by several observers led to conflicting opinions. At times there was nothing abnormal to be felt, while at others a mass of varying size could be palpated, sometimes on the right side, sometimes in the epigastrium. A barium enema was administered and the diagnosis was clearly revealed (Fig. 1). Laparotomy was performed on the third day. There was some excess of free fluid in the peritoneal cavity, the small bowel was somewhat dilated and many enlarged glands were present in the mesentery. Along the ascending colon a typical intussusception could be felt. While the bowel was being delivered this reduced itself except for an invagination of the caput caeci which was reduced by digital pressure. Marked thickening of the ileo-caecal valve could be felt through the caecum.

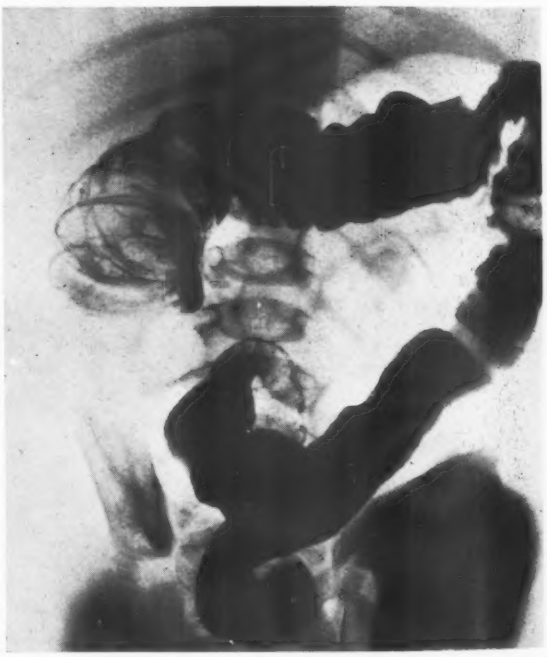

FIG. 1.—Barium enema in Case 1 showing typical cupola appearance.

The appendix was bound down to the lateral wall of the caecum and enveloped in fine adhesions. It was thought that this tethering of the caecum by the appendix was the reason why the intussusception had not progressed in the usual manner. Appendicectomy was carried out. Apart from an attack of diarrhoea due to a specific coliform organism on the tenth day the subsequent course was satisfactory, and when last seen the child had a soundly healed wound, no symptoms, and was gaining weight.

Case 2. A girl was first seen at the age of 3 months because she had a large tongue which protruded all the time. She appeared to be a cretin and treatment with thyroid was begun. She progressed fairly well for the next three months and then began to vomit once or twice a day. This was associated with attacks of abdominal pain which were brief and between which she seemed to be well. This state persisted for three weeks during which time the stools were dark brown, slimy and loose. The day before she was admitted (at the age of 7 months) the attacks of 'colic' were much more frequent and severe and in some of them she went into opisthotonos. From the onset of the vomiting she had lost ½ lb. in weight. When she was examined a mass was felt in the left hypochondrium. It was difficult to define and was thought to be the spleen. The liver was easily palpable. A bowel wash-out was given and thereafter the mass could no longer be felt. A barium enema was attempted on two occasions but the barium was repeatedly rejected and the examinations were inconclusive. In the course of the next few days the infant developed a respiratory infection which was treated with penicillin. Vomiting persisted and, though she did not have any attacks of severe pain, she was occasionally cross and fretful without apparent cause. She tended to be constipated and required aperients but the stools were not otherwise abnormal. For three weeks she remained much the same and then suddenly became acutely and seriously ill. She vomited continuously, passed frequent small stools consisting almost entirely of blood and mucus, and rapidly became drowsy and dehydrated. A mass could be felt in the left hypochondrium similar to that felt at the time of admission. A barium enema revealed complete obstruction to the flow of the barium at the lower end of the descending colon (Fig. 2). Laparotomy was performed six weeks after the onset of the first abdominal symptoms. In the left side of the abdomen a mass was felt which had the characteristics of an intussusception but which was pointing upwards instead of downwards. The bowel was delivered and in the middle of the transverse colon a retrograde colo-colic intussusception was found. This was reduced without much difficulty. A further intussusception was found in the ascending colon, the apex having travelled as far as the hepatic flexure. Reduction of this second intussusception was easily accomplished as far as the caecum, where it was found that the appendix had intussuscepted on itself and was invaginated into the caecum. The appendicular intussusception was irreducible and during attempts to reduce it the caecum was perforated. Resection of the appendix with a small part of the caecum was performed and the resulting defect closed in two layers. Fig. 3 represents the state of affairs in this child's abdomen at the time of operation. There were in fact three intussusceptions, of which the appendicular one was probably of long standing, the ileo-colic one was probably recurring, and the colo-colic one of recent onset and the cause of the sudden deterioration in the child's condition. The post-operative course was uneventful apart from an attack of chickenpox and there have been no further abdominal symptoms.

FIG. 2.—Barium enema in Case 2 showing complete obstruction to flow of barium at lower end of descending colon.

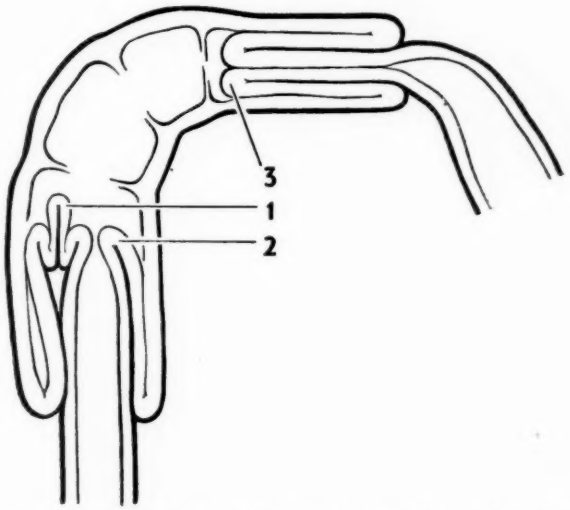

FIG. 3.—Condition found at operation in Case 2, showing three intussusceptions present at the same time.

Discussion

The first of these cases presented no unusual features apart from the long duration of the symptoms. The second case, on the other hand, was quite remarkable not only for the length of the history but for the presence of three intussusceptions at the same time, the occurrence of a retrograde intussusception (an extremely uncommon event during life) and the appendicular intussusception (also a rare occurrence).

In order to discover how frequently intussusceptions of such prolonged course occur in children the records of the three hospitals in Manchester which admit large numbers of children were examined. The numbers are shown in Table 1. In the

TABLE 1

INTUSSUSCEPTION IN THE THREE MAIN CHILDREN'S HOSPITALS IN MANCHESTER

Hospital	Up to 1948	1948	1949	1950	1951	1952	1953	To mid-1954	Total
R.M.C.H.		17	5	12	10	10	11	4	
B.H.H.			23	29	19	26	20	11	
D.Y.H.	29	1	12	7	8	10	4	5	
Total ..	29	18	40	48	37	46	35	20	273
			M = 41						

five years for which complete records are available the average number of cases of intussusception per year is 41. This is comparable to the numbers reported by Spence and Court (1950) in Newcastle (239 cases in six years).

It was soon obvious from a scrutiny of these records that a definition of what constitutes a case of subacute or chronic intussusception was required. There is evidence from the early literature, before surgical treatment was practised, that the average duration of the illness from the onset of symptoms until death in cases of acute intussusception was four days (Hutchinson, 1874). Pilz (1870) reviewed all the cases of intussusception in children reported up till that date and he noted that in the great majority death occurred between the second and sixth days. It seems clear that the ordinary case of acute intussusception will die within a week of the onset unless treated and that survival beyond the sixth day constitutes evidence of chronicity. This is in accord with the classification of Rafinesque (1878) who divided intussusception into four types, hyperacute (dying within two days of the onset), acute (dying within a week), subacute (surviving for seven to 14 days) and chronic (surviving more than 14 days). The records of the 273 Manchester cases have been analysed from this point of view. Table 2 gives the results of this analysis.

TABLE 2

INCIDENCE OF SUBACUTE AND CHRONIC INTUSSUSCEPTION IN MANCHESTER SERIES

	Total Cases	Subacute — 7-14 Days	Chronic — Over 14 Days	Subacute + Chronic
Under 1 yr.	195	2	5	7 (3·6%)
Over 1 yr.	78	7	1	8 (10·3%)
All ages	273	9	6	15 (5·5%)

As a check on these figures a number of large reported series have been examined. Series based on less than 100 cases have been ignored as likely to be misleading in assessing the incidence of a rather uncommon feature like chronicity. Fifteen reports were satisfactory as far as total numbers were concerned but in only six of them was there information about the length of history suitable for the present purpose (Pitts, 1901; Koch and Oerum, 1912; Clubbe, 1921; Stallman, 1926; Ladd and Gross, 1934; Nyborg, 1943). These series comprise a total of 1,352 cases, and Table 3 shows the incidence of chronic intussusception in this number. 'Chronic' in this case indicates survival beyond six days from the onset; it was not possible on the available data to subdivide these further into subacute and chronic types. The agreement with the Manchester figures is close and it seems justifiable to combine the two sets of figures as shown in the last column of Table 3. It then appears that in

TABLE 3

INCIDENCE OF 'CHRONIC' INTUSSUSCEPTION IN SIX REPORTED SERIES COMPARED WITH MANCHESTER SERIES

	Manchester	Former Series	Total
Under 1 yr. ..	7 of 195 (3·6%)	29 of 956 (3·0%)	36 of 1,151 (3·1%)
Over 1 yr.	8 of 78 (10·3%)	41 of 396 (10·4%)	49 of 474 (10·3%)
All ages	15 of 273 (5·5%)	70 of 1,352 (5·2%)	85 of 1,625 (5·2%)

infants under 1 year about 3%, and in older children about 10%, of intussusceptions run a prolonged course. If this is accepted the probability of encountering such a case can be estimated. In Manchester each year there are about 40 cases of intussusception of which 30 are infants. That means that there is likely to be one case of chronic intussusception in an infant each year. Since these cases are seen in three different hospitals and treated by several surgeons the probability of any one surgeon seeing a case is small. Although the incidence of chronicity is greater in older children the total number of cases of intussusception in them is so much smaller that again the chance of any one

person seeing a case is slight. The frequency works out at about one case a year in the city of Manchester.

These figures do not support the opinions quoted in the introductory paragraph about the extreme rarity of this disease in children. However, there is further support for our position in the paper of Birkenfeld (1926). He was able to find reports of 160 cases of intussusception in children under the age of 14 years in whom the duration of symptoms was 14 days or longer. Of this total 31 were infants under the age of 1 year. Since Birkenfeld wrote there have been several papers on chronic intussusception in children, most of which treat the condition as one of great rarity. Birkenfeld's paper does not seem to be as widely known as it ought to be.

The symptoms in the cases occurring in Manchester are shown in Fig. 4. They do not differ

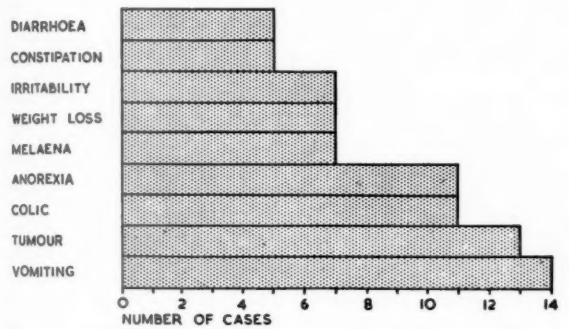

FIG. 4.—Analysis of symptoms in 15 cases of subacute and chronic intussusception.

appreciably from those to be expected in any case of intussusception and we should like to emphasize the contention of Birkenfeld and of Garvie and Kemp (1945) that the most significant feature of the history in these cases is the occurrence of intermittent, colicky abdominal pain. 'The only reliable clinical feature is a story of repeated attacks characterized by the sudden onset of gripping abdominal pain. All other symptoms of intussusception may be absent and are unreliable' (Garvie and Kemp).

Summary

Two cases of intussusception in infants, of prolonged duration, four and six weeks respectively, are reported in detail.

From an analysis of hospital records it is concluded that the incidence of prolonged intussusception is about 3% of all cases in infants under 1 year of age and about 10% in children over that age. These figures are in substantial agreement with those derived from a review of the literature.

Subacute and chronic intussusception in infants and children is not such a rare condition as is often claimed.

We are indebted to the medical staffs of the hospitals whose records we have consulted for permission to do so.

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GANGRENE OF THE EXTREMITIES IN TWO AFRICAN INFANTS

BY

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Gangrene of the extremities in infancy and childhood is a rare condition which has aroused the interest of previous clinicians because of its diverse and obscure aetiology. The two cases recorded here presented a very similar clinical picture in that the gangrene occurred in association with an acute gastro-intestinal infection.

Case Reports

Case 1. A male Mkamba child aged 5 months was admitted to King George VI Hospital, Nairobi, on March 24, 1954, with a history of diarrhoea and vomiting of three days' duration.

On admission the child appeared well nourished but was dehydrated and toxic: the temperature was 97° F. (36·1° C.), pulse 120/min., respirations 28/min. Examination of the ears, throat, chest, and cardiovascular systems revealed no abnormalities. The mouth was dry and the abdomen lax and sunken. An intraperitoneal infusion of 0·45% saline with 2·5% glucose (270 ml.) was given, gastric lavage performed, and feeding with Hartmann's solution started. Sulphaguanidine, 0·5 g. six-hourly, was given by mouth and retained. Six loose green stools were passed during the next 12 hours, but a stool culture yielded no pathogenic organisms. No malarial parasites were detected in the blood slide.

By March 26 the hydration had improved, diarrhoea had decreased, but vomiting persisted. The child held himself stiffly and resented any interference. Although no fresh clinical signs were detected and the child remained afebrile, a course of penicillin, 20,000 units daily, was introduced. Lumbar puncture was performed and yielded a clear colourless fluid under normal pressure: cells, 10 lymphocytes per ml.; protein, 160 mg. %; chlorides, 970 mg. %; sugar, 156 mg. %. No organisms were detected. In view of these findings a further intraperitoneal drip was given and the child's condition improved. Apart from occasionally vomiting sulphaguanidine, he retained feeds, and the diarrhoea subsided. On March 29 the temperature rose suddenly to 103° F. (39·4° C.), and gangrene of both hands and the left ear was noticed. There was a clear line of demarcation at the junction of the ear and the scalp, and across the palms of both hands. Vomiting began again and the child died the same evening.

Post-mortem examination revealed a terminal bronchopneumonia involving both lungs. The peritoneal cavity contained no free fluid and showed no evidence of inflammation. There was moderate congestion of the intestinal tract, but no mucosal ulceration. No abnormality was detected in the heart or great vessels, and no macroscopic thromboses or emboli in the peripheral vessels. Unfortunately in this case no sections of blood vessels were taken for microscopic examination.

Case 2. A female Kikuyu child aged 3 months was admitted to King George VI Hospital, Nairobi, on May 23, 1954, with a history of diarrhoea for the past 36 hours. The stools were loose and had been noticed to contain blood and mucus. On admission she appeared toxic and moderately dehydrated, with loss of tissue turgor. Her temperature was 98° F. (36·7° C.), pulse 100/min., respirations 24/min. No abnormalities were detected in chest, cardiovascular system, throat, or ears. The abdomen was soft and peristalsis active. A stool culture on admission yielded *Shigella flexneri*. An intraperitoneal drip of 0·45% saline with 2·5% glucose (270 ml.) was given, and sulphaguanidine, 0·5 g. six-hourly, was taken by mouth. Hourly feeds of glucose saline were taken well and retained, but as hydration was unsatisfactory a further intraperitoneal drip was given on May 24. By May 27 the hydration had improved, but the child remained toxic and the diarrhoea persisted. On the morning of May 28 she developed gangrene of both feet and the right hand with a clear line of demarcation at ankles and wrist. By this time her general condition had improved considerably; she was feeding well, and the diarrhoea was less. As she showed every sign of immediate survival, and it was considered that the loss of both feet and the right hand would be an almost insuperable disability to an African girl in later life, it was decided to try heparin as a means of re-establishing the circulation. A regime of heparin, 1,000 units, together with penicillin, 100,000 units, six-hourly was therefore instituted. On May 29 it was noticed that the gangrene had spread above the right wrist, but the general condition gave no cause for concern until midday when the child suddenly collapsed and died.

At necropsy the body was that of a well-nourished child showing gangrene of both feet, the right hand, and

lower third of the forearm. Examination of the abdomen revealed acute congestion of the bowel. The mucous membrane of both large and small intestines was red and velvety, and there were numerous enlarged mesenteric nodes. The mucous membrane of the stomach was injected, and the stomach contained some altered blood. The peritoneal cavity contained no free fluid. The liver was pale and fatty, but the other abdominal organs showed no macroscopic abnormality. The lungs were healthy and aerated. There was no evidence of a congenital cardiac abnormality or thrombosis of the great vessels. Examination of the arterial system from the abdominal aorta to the dorsalis pedes showed no macroscopic evidence of thrombosis. A similar negative result was obtained on dissection of the right brachial and radial arteries. There was, however, thrombosis of the veins accompanying the peripheral arteries. The upper limit of the thrombosis coincided with the line of demarcation of gangrene in the feet, but extended about one inch (2·5 cm.) above the level of demarcation in the forearm. Serial sections of the peripheral veins and arteries showed recent thrombus formation in the veins, but no evidence of arterial thrombosis, arteritis, or periarteritis.

Discussion

A survey of the literature describing gangrene in the early years of life provides an interesting study in clinical pathology. The incidence of the disease seems to be relatively higher among newborn babies than in the later months of infancy, but there is no common causative factor in either group.

Heller and Alvari (1941) report one case and have reviewed 39 other cases among newborn babies. Six were thought to have resulted from infection, five from pressure, seven from a possible Raynaud's disease or other neurological disorder, four from thrombosis, and one each from a doubtful syphilis and diabetes. In the remainder the cause was obscure. The suggested aetiology in their own case, which recovered, was that there has been an 'intimal agglutination' in the artery, which eventually became recanalized due to the pulsating column of blood acting proximal to the occlusion.

Other cases in infants have followed thrombosis and pressure (Brown and Smith, 1951), embolism or thrombosis from congenital heart lesions (Craig and Muns, 1931; Hansen, 1949), extension of the normal process of umbilical closure to involve the common iliac and hypogastric arteries (Garrod, Batten, and Thursfield, 1949), local infection (Alders, 1954), proved syphilis (Foster and Taylor, 1949), the inadvertent injection of nikethamide into the umbilical artery (Mills, 1949), and systemic infection in which microscopic inflammatory changes were observed in the arteries after death (Dohan, 1934).

Among the cases recorded in later infancy and childhood, systemic infection seems to play a greater part. In the series of von Khantz (quoted by Heller and Alvari, 1941) 39 cases were directly attributable to such infections as diphtheria, typhoid fever, scarlet fever, syphilis, pneumonia, measles, and enteritis. Similar findings have been recorded by Martin and Shore (1928), who reported four cases following diphtheria, pericarditis, indolent ulceration of the foot, and chronic tuberculosis respectively. In these cases a local endarteritis was demonstrated microscopically and occurred above the line of demarcation of the gangrene. Hoyne and Smollar (1941), who reported a case of gangrene associated with scarlet fever, also demonstrated arterial changes in the nature of a periarteritis. Lewis (quoted by Gelfand, 1947) described a bilateral symmetrical gangrene of the digits in childhood which was frequently associated with malnutrition, chronic ill health, or acute infection. The onset was sudden, the gangrene dry, and it was thought to be due to damage to the intima of the digital arteries causing thrombosis, although the main arteries to the limbs were unobstructed.

Gelfand (1947 and 1949) reported eight cases of symmetrical gangrene in adult Africans, thought to be due to a nutritional disturbance of the vessel wall leading to a vascular occlusion and gangrene. He also recorded one case in an African child in which thrombophlebitis was the causative factor. A recent case report published by Said (1954) of gangrene in a Malayan child presented a very similar clinical picture to the present cases in that the spontaneous gangrene of the feet occurred during the course of a gastro-intestinal infection.

In assessing the possible cause in the present cases, several factors were taken into consideration: (1) the nutritional state of the infants; (2) the state of hydration; (3) the fact that the initial regime of treatment involved the use of an intraperitoneal infusion; and (4) the fact that both infants were suffering from a gastro-intestinal infection.

(1) Although malnutrition, both frank and subclinical, is often a complicating factor in African paediatrics, it is rarely seen in infants under 6 months unless the breast-milk supply is inadequate or the child is suffering from some debilitating disease. Both these infants were well nourished, the mothers had adequate milk, and there was no previous history of illness. Gelfand's theory of nutritional vascular changes was therefore considered inapplicable.

(2) Spontaneous venous thrombosis is known to occur in severely dehydrated infants, particularly in the sluggish venous sinuses in the brain. It was thought at the time, and without any previous

experience of infantile gangrene, that a peripheral thrombosis due to dehydration had been the operative factor in Case 1, but the fact that the child's hydration had improved considerably 48 hours before the onset of the gangrene made the conclusion unsatisfactory. It is noted by Foster and Taylor (1949) that such peripheral circulatory disorders, when they do occur in infants, are often of a temporary nature and that the changes are usually reversible.

(3) Intraperitoneal infusions have been used in this hospital for approximately two years with very satisfactory results, and in no case has death or any serious complication been directly attributable to this form of therapy (Carter, 1953). It has been stressed, however, that it is essential to have the fluid warmed to body heat before transfusion in order to prevent the occurrence of shock in an already cold and dehydrated child. It was thought possible, therefore, that the introduction of cold fluid into the peritoneal cavity might have produced spasm in the large vessels of the posterior abdominal wall, thus precipitating thrombosis in an already sluggish circulation. This factor was thought worthy of consideration because in both cases there was reason to doubt whether the technique of transfusion had been faultless: in Case 1 the first drip was undertaken hurriedly owing to a delay in obtaining the saline, and in Case 2 the first drip was given as an emergency measure in another ward, unaccustomed to the technique, before the child was transferred to the children's ward. But, as both infants had had further intraperitoneal therapy under adequate supervision and did not develop gangrene until five days thereafter, it is doubtful if this could have been the sole factor in precipitating the condition.

(4) In previous cases of gangrene associated with acute infections, the condition is said to have been due to thrombosis following a toxic arteritis and this has been proved histologically in several instances. It is thought that circulating toxins or micro-organisms cause damage to the endothelial lining of the vessel walls with subsequent thrombosis. Normally the arterial stream would be too rapid to permit prolonged contact of micro-organisms with the vessel walls sufficient to produce damage, but in the capillary network and vasa vasorum the stream is much slower, and it is presumed that the process of thrombosis starts in these minute vessels and eventually spreads to involve the arterioles (Martin and Shore, 1928).

Conclusion

From the foregoing résumé of the literature and in the absence of any other demonstrable cause, it is suggested that gangrene in the cases here reported was due to a capillary thrombosis in which both spasm and infection played a part.

Summary

Two fatal cases of peripheral gangrene occurring in African infants suffering from gastro-enteritis are described. The literature relating to peripheral gangrene in childhood is briefly reviewed.

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A CASE OF FIBROMA OF THE LEFT VENTRICLE IN A CHILD OF 4 YEARS

BY

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(RECEIVED FOR PUBLICATION JUNE 30, 1954)

In view of the rarity of primary benign tumours of the heart, particularly of fibromata, the following case of mural fibroma of the left ventricle and interventricular septum seems worth recording.

Case Report

L.M., aged 4, was admitted to hospital with a diagnosis of paroxysmal tachycardia. She had been perfectly well until two days before admission when she developed a cold, became listless and refused food. On the day of admission she started to vomit and the general practitioner was called in. He found a heart rate of about 200 beats per minute and sent her into hospital.

Her early history was entirely normal; she was the first child of healthy parents, and a brother of 6 months is quite well. She had been seen by doctors at the infant welfare clinic, and at home during an attack of measles, and no suggestion of cardiac abnormality had ever been made.

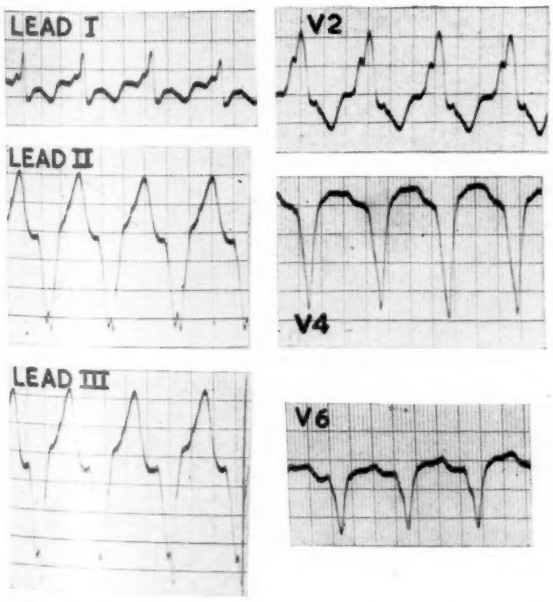

FIG. 1.—E.C.G. taken on admission showing paroxysmal ventricular tachycardia.

On admission she was very quiet and sweating profusely, but was not distressed. Her pulse was uncountable and the apex rate about 180 per minute. The apex beat was diffuse and the left border of the heart

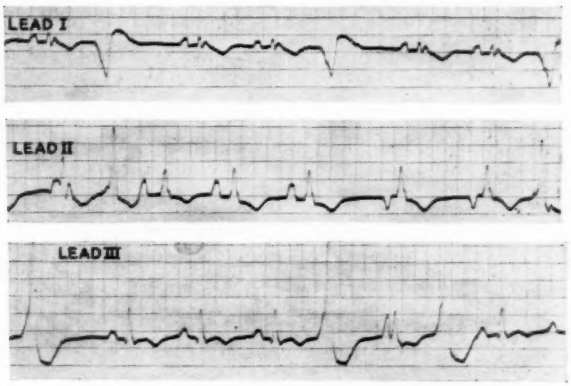

FIG. 2.—Taken after termination of initial paroxysm, showing T wave inversion in all leads, prominent P waves and multiple ectopic beats.

displaced 1 in. to the left of the midclavicular line. No murmurs could be heard. The blood pressure was 90/50 mm. Hg and there was no evidence of congestive cardiac failure. All other systems were normal and she was afebrile. An electrocardiogram (Fig. 1) showed a rapid rate and an abnormal rhythm. There was considerable doubt and difference of opinion both at the time, and later, as to whether the tracing showed auricular or ventricular tachycardia, but subsequent events suggest that it was probably ventricular.

The effect of vagal stimulation was first tried with no success, and the child was then given 'digoxin', 0·125 mg. orally, repeated in four hours. This had no effect and 'quinidine' was tried next and 100 mg. ($1\frac{1}{2}$ grains) was given two-hourly for three doses, without effect, and both drugs were then repeated in the same doses; again without effect. By this time, three days after admission, the heart was further enlarged to the left and the liver palpable $\frac{1}{2}$ in. below the costal margin, but there was no oedema, and the jugular venous pressure was not raised. It was decided to try intravenous procainamide, and in the next 20 hours three doses of 200 mg., 250 mg.,

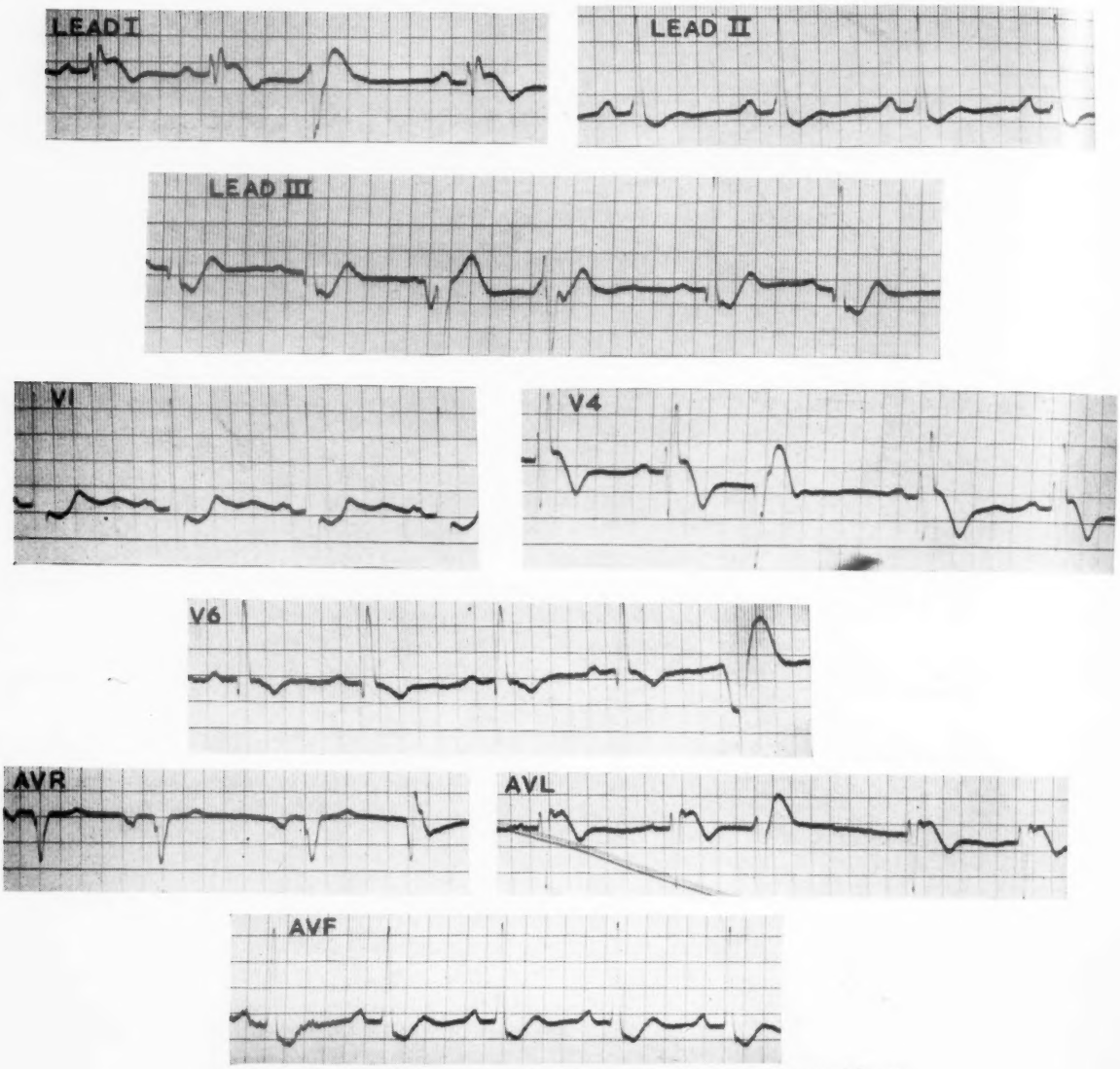

FIG. 3.—Showing displacement of the ST segment, with occasional ectopic beats.

and 200 mg. respectively were given slowly with continuous electrocardiographic and blood pressure recordings. The heart rate was slowed slightly to about 140 per minute but there was no change in the character of the tracings. The systolic blood pressure did not fall below 70 and rose again quickly after the injection.

Four days after admission she was given 0·25 mg. of 'digoxin' intravenously and within two hours her heart rate dropped to 90 per minute. An electrocardiograph (Fig. 2) showed sinus rhythm with multiple ectopic beats. The P waves were large and the T waves inverted in all leads. Digoxin was continued orally in doses of 0·125 mg. at first, four-hourly, and then at intervals of eight hours.

Forty-eight hours after the termination of the first attack she again developed tachycardia and an E.C.G. showed a reversal to the same abnormal rhythm. Again 'digoxin', 0·25 mg. intravenously, terminated the attack.

During the next four weeks further paroxysms occurred and it was not found possible to discontinue the 'digoxin'. Increasing doses were necessary and she was finally controlled on 0·25 mg. twice daily. During this time repeated E.C.G. tracings were taken. The initial T wave inversion in all leads disappeared in a few days and was attributed to functional changes in the myocardium secondary to the prolonged attack of tachycardia. The P waves also became less prominent. Multiple multifocal ectopic complexes continued to be seen and progressive ST changes were noticed, especially in the anterolateral and left ventricle surface leads; this was taken to indicate extensive myocardial necrosis in this region (Fig. 3). On one occasion a tracing included a

change-over from ectopic to sinus rhythm (Fig. 4) and showed very clearly the multifocal nature of the disturbance of the rhythm.

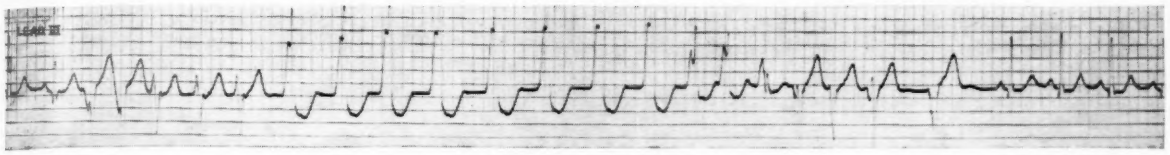

FIG. 4.—Lead III taken just after a further attack of paroxysmal tachycardia showing the change from abnormal to sinus rhythm, and the multifocal nature of the ectopic beats.

Radiographs showed a grossly enlarged left ventricle with a small area of calcification in its centre (Figs. 5 and 6). All other investigations, including blood films, sedimentation rates, blood chemistry and radiography of long bones, were normal.

An attempt was made to control the ectopic beats by adding 'quinidine', 200 mg. (3 grains), three times a day. This was, however, only partially successful, and after four months in hospital she was sent home on digitalis and 'quinidine', as it was felt that the prognosis was very grave. She remained at home for about three weeks only as she was vomiting and seemed ill and unhappy, and was therefore readmitted. No obvious change was noticed in her clinical condition but the E.C.G. showed further changes in the ST segment (Fig. 7). Four days after admission she died suddenly in her sleep.

MORBID ANATOMY. At necropsy nothing abnormal was found outside the heart; this was enlarged and grossly abnormal in appearance. The anterior aspect presented an irregular, whitish, nodular appearance (Fig. 8) and was the site of a tumour measuring 6 cm. × 5 cm. × 4 cm. The origins of the great vessels were all normal and the coronary arteries were normal in origin and distribution but followed a tortuous course. A radiograph of the heart after removal and before section showed many specks of calcification; the largest was identified as the area of calcification visible in chest radiographs taken during life (Figs. 5 and 6).

On section the tumour presented the dense, white, whorled appearance seen in uterine fibromata (Fig. 9) and there was no definite capsule. A histological section shows a cellular fibroma which seems to be innocent although the myocardium appears to be almost strangled by the growth. Small islands of residual cardiac muscle can be seen scattered throughout the substance of the tumour (Fig. 10).

The diagnosis of a tumour was not made during life. The most favoured suggestion had been fibro-elastosis of the left ventricle, as it was felt that this would account for the left ventricular damage and possibly for the widespread disturbance of conducting tissue. Against this were the age and previous normal health of the child. Other possibilities considered were acquired coronary artery occlusion, and an anomalous origin of the left coronary artery from the pulmonary trunk; but neither was thought to fit the picture at all closely.

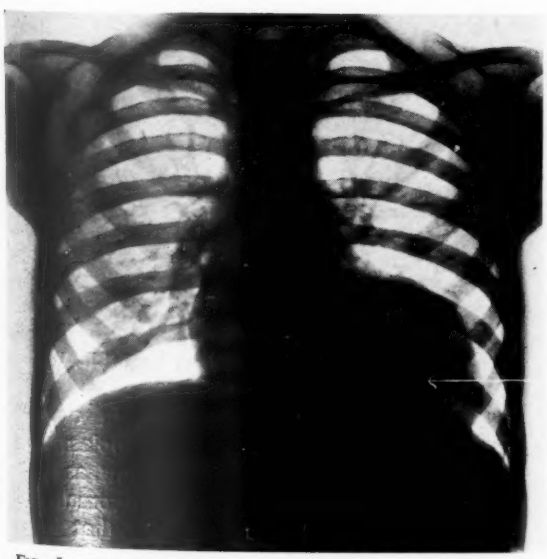

FIG. 5.—Enlargement of the left ventricle with an area of calcification.

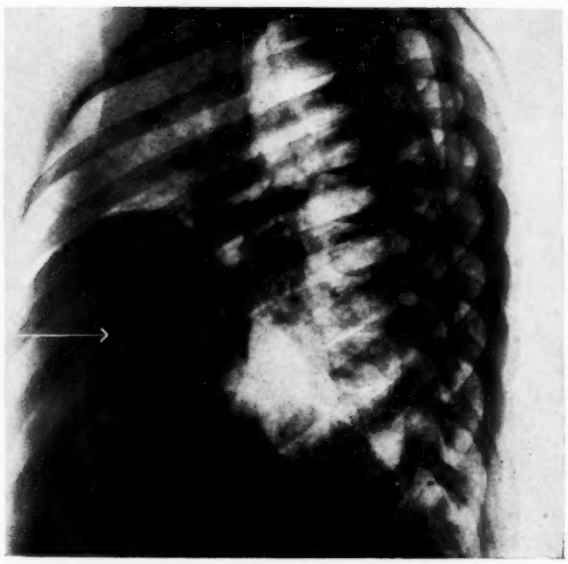

FIG. 6.—Oblique view showing the tumour 'end on'. Calcification is visible as a horizontal line.

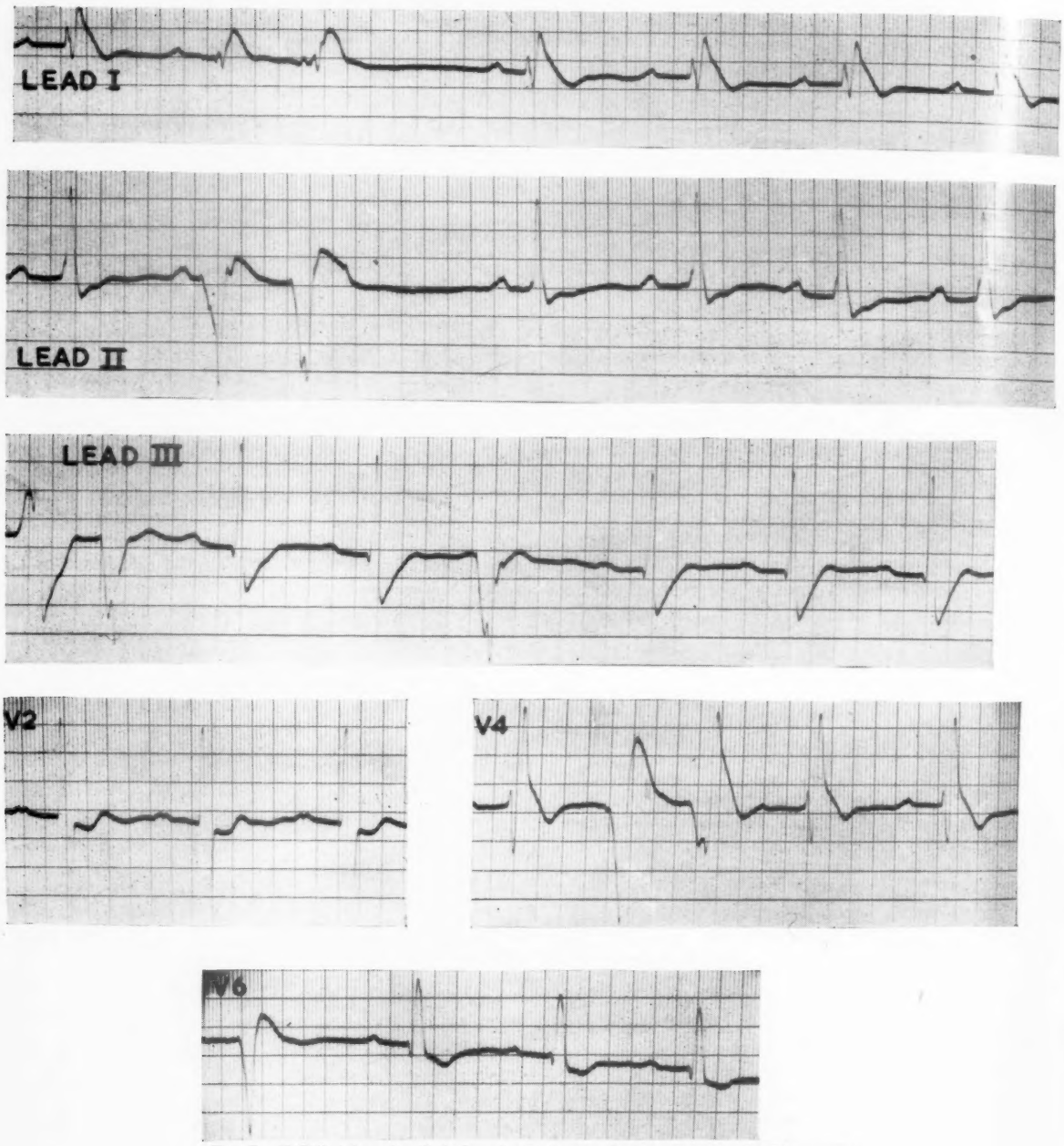

FIG. 7.—E.C.G. taken shortly before death showing further alteration in ST segment.

Discussion

Cardiac tumours are rare, and Yater (1931) recorded 150 primary cases from the literature of which about 20% were malignant. Mahaim (1945) collected 456 primary tumours from the literature, and attributes the first description of a fibroma to Colombo in 1559. In all Mahaim was able to collect 37 recorded cases of fibroma of which eight were polypoid and 29 non-polypoid, though many of these are without histological proof.

Considerable controversy has arisen over the aetiology of primary benign cardiac neoplasms, and some authors will not accept a fibroma as a true tumour. Prichard (1951) classes fibromata and hamartomata together, pointing out that in the heart a hamartoma may be composed of muscle, fibrous tissue, endothelium, blood vessels, fat,

nerves, or a combination of these elements. If this view is accepted then some myxomas, lipomas, and all of the rhabdomyomas and angiomas could be included in this category. However, most cases reported as hamartomas most closely resemble fibromas. Mahaim (1945) does not agree with this concept and classifies fibromata as polypoid, mural, and a third category of fibrous papillomata on the valves giving rise to valvular murmurs.

We have reported our case as a fibroma in view of the white whorled appearance of the tumour which had no definite capsule, and the typical histological picture. The presence of mucin and elastic tissue were excluded by specific staining methods.

FIG. 8.—Anterior surface of the heart and lungs, showing the surface of the tumour.

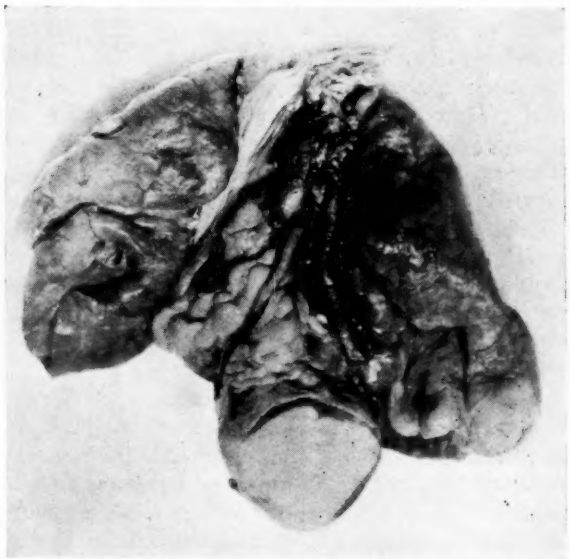

FIG. 9.—Anterior surface of the heart with a section of the tumour removed showing dense, white tumour tissue surrounded by a narrow edge of muscle.

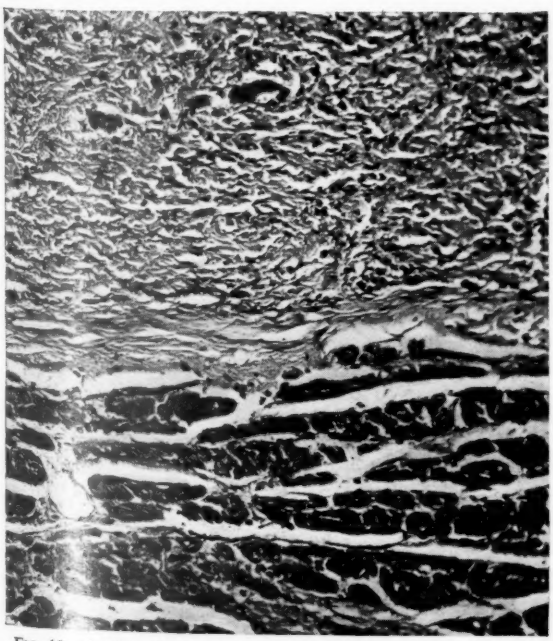

FIG. 10.—Section showing tumour and cardiac muscle. × 120.

FIG. 11.—Section of tumour. × 260.

The recognition of cardiac tumours in life is difficult. Yater (1931) divides cases into two clinical groups. The first group present with terminal heart failure, sudden death or symptoms suggestive of bacterial endocarditis, and the second group suggest the presence of a cardiac tumour by virtue of heart block, cardiac dysfunction without apparent cause in a patient known to have a malignant process, haemorrhagic pericardial or pleural fluid, or suggestive radiological appearances. The clinical picture must depend upon whether the tumour is polypoid when it may give rise to signs and symptoms of valvular obstruction or incompetence. The mural tumours are more likely to interfere with the conducting system of the heart. Angiocardiography might be helpful in cases where a chamber of the heart is distorted, and in our case it is probable that the left ventricular chamber would have appeared small and misshapen. This, taken in conjunction with the radiological appearances of the apparent large left ventricle, could have given us valuable help.

Mahaim reports a case of intramural fibroma discussed by Macherey (1937) in which there was calcification visible on radiographs. Pfeiffer (1952) states that radiological findings of masses or unusual contours of the heart not easily explicable and unexplained or atypical alteration in rate or rhythm on the electrocardiogram with a tendency to rapid and sudden changes in the degree and type of aberration, or electrocardiographic changes suggestive of coronary occlusion, may lead to the recognition of a cardiac neoplasm. In our case an unusual contour of the heart was visible together with calcification; the electrocardiogram showed alteration of rate and rhythm and the later findings were suggestive of coronary occlusion. Unfortunately these findings did not lead us to a diagnosis during life.

Siegel and Young (1933) report a case of tumour affecting the left ventricle and septum in which the electrocardiogram at first suggested myocardial damage from coronary disease, despite the negative history of the patient. The T waves were constantly inverted in all leads, and their direction was not reciprocal in leads I and III as is usual in recent coronary thrombosis, and also there were no day-to-day changes. Other authors (Lloyd, 1929; Willius and Amberg, 1930; Houck and Bennett, 1930) describe electrocardiograms associated with cardiac neoplasms, and in all the rhythm was normal, but there was no constancy of the isoelectric level in the ST segment.

Rosenbaum, Johnston, Alzamora and Mich (1944) reported a case of extensive secondary carcinoma involving the left ventricle and most of the right ventricle in which serial electrocardiograms showed persistent upward displacement of the RS-T segment in leads II, III and V_F, and in a number of unipolar leads. They attribute these changes to the continuous acute myocardial injury as the neoplasm infiltrated the cardiac musculature.

Electrocardiograms are not available for many recorded cases of primary heart tumours since many have had no cardiac symptoms and the tumour has been found unexpectedly at necropsy.

Summary

A case of mural fibroma of the left ventricle in a child of $4\frac{1}{2}$ years is described, and is discussed in relation to diagnosis during life. The literature on primary benign cardiac neoplasms is briefly reviewed, and the recognition and treatment of such tumours is discussed.

Our thanks are due to Dr. B. J. Haram who performed the necropsy, and to Dr. R. E. Bonham Carter and Dr. Paul Wood for helpful advice in the management of the case.

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FAMILY PERIODIC PARALYSIS IN A MENTALLY DEFECTIVE BOY

BY

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From the Baldovan Institution, by Dundee

(RECEIVED FOR PUBLICATION JULY 26, 1954)

Family periodic paralysis is a condition characterized by periodic attacks of flaccid paralysis of the striated musculature accompanied by loss of tendon reflexes. Until recently the cause was unknown, but studies by Aitken, Allott, Castleden and Walker (1937) have correlated variations of the plasmo-serum potassium levels with the attacks of paralysis. In the case then studied the critical plasmo-serum potassium levels were considered to be 12 mg./100 ml., when marked muscular weakness occurred, and 10 mg./100 ml., below which paralysis was observed. A fall in the plasmo-serum potassium level can be brought about in the normal person by large doses of glucose orally, the injection of insulin, or a combination of both. It appears that in susceptible subjects this reaction is much exaggerated. The condition was regarded as familial by Holtzapple (1905), who traced its incidence through several generations and considered transmission of the condition possible by either parent with an increased incidence of affected males. Although the disease may be traced through several generations, a generation may escape and the condition appear in the next. Holtzapple thought that family periodic paralysis may occur in association with a family history of migraine, and suggested that migraine might represent the equivalent of a paralytic attack. Only two post-mortem examinations appear to have been carried out, but nothing of significance was found in the nervous or muscular systems.

Case Report

The case recorded is that of a mentally defective boy, aged 16 when first observed. He is of imbecile grade with a residual left hemiplegia resulting from a birth injury, and is also subject to grand mal episodes. Following admission to the institution it was noted that his 'fits' fell into two distinct types: (1) typical grand mal attacks and (2) episodes of extreme flaccid paralysis of the limbs and trunk. Initially it was considered that the paralysis was a post-epileptic phenomenon. After careful observation, during which control of the grand mal episodes was established by the administration of phenytoin sodium (1½ gr. (0·1 g.) t.i.d.), it was noted that the episodes of paralysis were unconnected with grand mal attacks and that paralysis mainly occurred when the patient awoke in the morning. Eventually one paralytic episode was observed in its entirety.

Initially the patient became apprehensive and desired company; then he became elated and started singing. Swallowing movements and lip smacking were noted. His pupils became widely dilated and did not react to light. During this stage the patient was sitting up in bed moving his limbs normally. Speech became quite unintelligible and slurred, and his whole appearance suggested drunkenness. Shortly afterwards voluntary movements became much diminished, and he became distressed, carrying out rubbing and scratching movements over the left chest. Respiration became irregular, periods of air hunger alternating with rapid, shallow respirations. Gradually all movements of the limbs ceased, but the hands and feet did not appear to be affected, the right hand continuing the rubbing and scratching movements. During the fully developed paralytic stage the patient lay in bed, moving his hands and feet and speaking incoherently, but unable to raise his head from the pillow or his limbs from the mattress. Skin sensation was normal. Cutaneous and tendon reflexes were completely absent, though earlier in the attack an extensor plantar reflex was observed. The pulse rate fell to 58, but heart action remained regular with no adventitious sounds. There was no cyanosis. The patient then, by hand signs and facial expression, showed an obvious desire to use a urinal, but although the desire to pass urine was obviously strong he was unable to do so. Skin temperature was low. The paralytic period continued for two and a half hours, during which the patient perspired freely, particularly in the head and face areas. He suddenly passed about 11 oz. (312 ml.) urine and appeared much brighter; his pupils returned to normal size and reacted to light. Within 15 minutes he was sitting up in bed and reaching for sweets on a window ledge near his bed.

In all, 24 such attacks have been observed over the past six months, the shortest lasting half an hour, the longest 48 hours. The pattern of all the attacks has been similar to that initially observed. It has also been noted that when the patient is confined to bed and sleeping

during the daytime the attacks bear a relation to sleep, 19 having occurred on waking as opposed to five while the patient was ambulant.

During attacks all tendon and cutaneous reflexes are lost, and there is no muscular response to mechanical stimulation. Cutaneous sensation appears to be unaltered. The cranial nerves are unaffected. Plasmo-serum potassium during the flaccid phase was estimated at 8·5 mg./100 ml., the normal value in this patient being 17·5 mg./100 ml. Urine examination revealed no abnormal constituents before or after an attack. Once the diagnosis was made treatment was instituted according to that carried out by Herrington (1937). At the start of the attack 10 g. potassium citrate was given orally, followed by 5 g. at 15-minute intervals. Recovery ensued within 20 minutes in all attacks when potassium citrate was administered. It was found empirically that a single dose of 10 g. of potassium iodide produced the same result.

In order to establish a diagnosis it was decided to apply the findings of Aitkin *et al.* regarding the patient's reaction to oral glucose and the injection of insulin. Initially 50 g. of glucose was given orally, and this dosage was repeated at half-hourly intervals. No paralytic episode occurred, but the boy exhibited the clinical signs of an impending attack, reaching the 'drunken' stage. The administration of 5 units of soluble insulin, however, precipitated a full paralytic episode within 30 minutes, flaccid paralysis lasting 20 minutes.

Family History

Investigation into the family history produced two significant points: (1) there was no history of any comparable condition on the paternal side of the family, but (2) the patient's mother admitted to having suffered from severe headaches since childhood, as did the maternal grandmother. Unfortunately the cooperation of the family was not good and no further information could be obtained. The parents stated that the patient had had 'jerking fits' since early childhood, but that from about the age of 12 he had two kinds of fits, 'jerking ones' and 'floppy ones', which they considered were 'both the same thing' and had paid no particular attention to them.

Discussion

This interesting case brings several important points to notice: first, the existence of family periodic paralysis in association with major epilepsy, the onset of periodic paralysis being at about 12 years of age, and, secondly, the absence of any comparable episode affecting any recent members of the family for at least two generations, but with a history of severe headaches, highly suggestive of migraine, on the maternal side of the family in two generations. Initially the diagnosis was uncertain, as the paralytic episodes were attributed to a post-epileptic state until the epilepsy was controlled and a full paralytic episode was observed. The criteria for diagnosis were based on the findings of Aitken *et al.*, namely, a plasmo-serum potassium level of under 10 mg./100 ml. during the paralytic phase, the loss of tendon and cutaneous reflexes with retention of cutaneous sensation, and the loss of muscle response to stimulation. This case fulfils all these requirements. The administration of glucose orally does not produce the full syndrome, but is sufficient to initiate the early clinical signs of an attack. Insulin, however, precipitates a characteristic paralytic episode. The question of sphincter control is difficult to understand, but in this case the sphincter appears to be in spasm and urine cannot be passed voluntarily. Further involvement of the autonomic nervous system is shown by the size of the pupils, fall of skin temperature, and perspiration. The relaxation of the urinary sphincter and the return of the pupils to normal precede recovery from the attack. Treatment as recommended by Herrington (1937) produces rapid recovery, but why a smaller dose of potassium iodide should have a similar effect to a larger dose of potassium citrate is uncertain. The marked frequency of attacks following sleep is not understood, but may be due to change in the blood chemistry during sleep.

Summary

A case of family periodic paralysis is reported occurring in an epileptic mentally defective patient. The onset of paralytic episodes occurred at about 12 years of age. During the paralytic episode the plasmo-serum potassium level falls below 10 mg./100 ml. to 8·5 mg./100 ml. Flaccid paralysis of limbs and trunk occurs without the hands and feet being affected. There is no involvement of cranial nerves. Tendon and cutaneous reflexes are abolished during attacks, but cutaneous sensation is unimpaired. Muscular response to mechanical stimulation is lost. The autonomic nervous system is also involved, as demonstrated by the pupils, urinary sphincters, and skin. Rapid recovery follows the oral administration of either potassium citrate or iodide. The administration of glucose orally does not precipitate the full syndrome in this case, but the injection of insulin produces a paralytic episode. The incidence of attacks show a relation to sleep. There is no family history of family periodic paralysis as such, but there is a history highly suggestive of migraine in the patient's mother and maternal grandmother.

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PELLAGRA IN AN ENGLISH CHILD

BY

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From Odstock Hospital, Salisbury

(RECEIVED FOR PUBLICATION AUGUST 28, 1954)

Pellagra is very rare in this country except for occasional mild cases amongst elderly inmates of mental institutions (Hardwick, 1943). No case has been reported in a child since 1940, when Hope Simpson (1940) described the condition in an English schoolgirl aged 11 years, in whom the outcome was fatal.

A case of pellagra in a young child, due to an unusually fastidious appetite, is described below.

Case Report

In September, 1953, a girl aged 4 years and 9 months was admitted to hospital suffering from extreme weakness, a rash and mental confusion. In June, 1953, the commonest month, according to Goldberger, Wheeler, Sydenstricker and King (1929), for the onset of pellagra, her parents first noticed an erythematous rash on the cheeks and chin, quickly followed by a similar rash on the exposed parts of the arms and legs. The rash was persistent and noticeably worse after exposure to sunlight.

Soon after the development of the rash, she began to complain of attacks of dizziness, which recurred with increasing frequency in the ensuing weeks.

During the three weeks before admission, she became increasingly weak and spent most of her time either in bed or lying on a settee, unable to stand up for more than a few minutes.

Since June there had been a progressive loss of appetite and a loss of weight of 9 lb. There had been no vomiting or diarrhoea. There was a tendency to constipation. A little frequency of micturition occurred in the week preceding admission.

The patient lived with her parents and grandmother, all of whom enjoyed good health. An only child, she had never had a big appetite and since the age of 1 year she had refused to eat cereals, meat and all green vegetables.

A typical day's diet the previous winter had been:

Breakfast:	Boiled egg, bread and butter, tea.
Lunch:	Potatoes and gravy, occasionally carrots, fruit and custard or rice pudding.
Tea:	Bread and butter, cake, tea.
Supper:	Two biscuits, cup of milk.

Occasional extras were bananas, grapes, oranges, sweets, milk chocolate.

Virol, three teaspoonfuls daily, was given from November until March.

Her diet on the day before admission was:

Breakfast:	One slice buttered toast, 1 cup milky tea.
Mid-morning:	One tablespoonful of milk jelly.
Lunch:	One small potato, gravy made from meat, 1 tablespoonful of grated carrot, 1 dessertspoonful of stewed apple, small portion of custard.
Tea:	One small teacake with butter, 1 cup milky tea.
Supper:	One cup of milk, 1 biscuit.

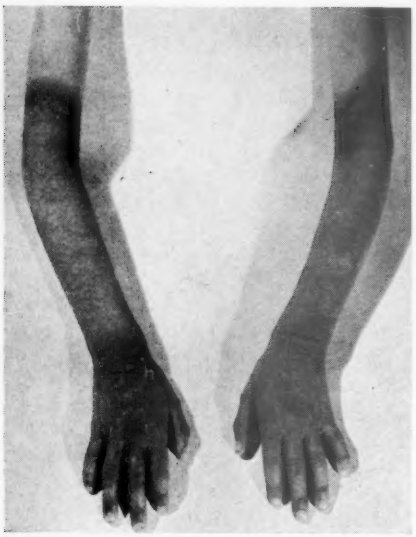
On admission, the patient was tall and thin (height 3 ft. 8 in., weight 2 st. 3½ lb.).

Her skin was strikingly dry. A darkly pigmented, thickened and hyperkeratotic condition was present, chiefly on the exposed areas. On the limbs, the affected areas followed a symmetrical 'stocking' and 'long glove' distribution. Isolated, similar patches were present on the buttocks. On the face, the distribution was of 'butterfly' type on the cheeks and dorsum of the nose and the sides of the chin were also affected. The neck was relatively unaffected.

FIG. 1.

The tongue was bright red, smooth and clean, with ulcers on the under-surface. The buccal mucous membrane was also bright red. No cheilosis was present. The teeth were sound.

The pulse rate varied from 100 to 145 per minute with normal rhythm. The apex beat was normal in position and the heart sounds were normal.



FIGS. 2 and 3.

Clinical examination of the lungs and abdomen showed no abnormality.

Tactile sense was impaired over the cutaneous lesions of the limbs, normal elsewhere. All tendon reflexes were sluggish but symmetrical. The abdominal reflexes were normal. Coordination was unimpaired. The cranial nerves were intact and the optic fundi normal. The child was cooperative but easily tired, with a poor faculty for concentration.

The blood picture and E.S.R. were normal. Serum protein was 6·0 g. % (albumin 4·4 g. %, globulin 1·6 g. %). Blood chemistry was otherwise normal.

The urine contained no albumin, but a little sugar (0·3%) was present, with some acetone. Phenyl pyruvic acid and porphyrins were absent from the urine.

Radiographs of the chest and wrists were normal. The electrocardiogram was normal.

The diagnosis of pellagra was made and treatment was begun with nicotinamide, 25 mg., three times daily by mouth. This was increased to seven times daily the following day. In addition, 'becosym', 2 ml. daily, was injected intramuscularly, and two 'adexolin' capsules were also given daily.

During the following few days intermittent diarrhoea and intermittent glycosuria (0·3%) occurred. According to Bicknell and Prescott (1953), impaired glucose tolerance is a regular finding in pellagra. Glucose tolerance tests were carried out and showed impaired tolerance. Glycosuria ceased after two weeks, and a glucose tolerance test after three weeks gave a normal result.

Two days after the start of treatment mild mental confusion persisted but an improvement in the cutaneous lesions was already noticeable. The knee jerks were found to be slightly exaggerated and ankle clonus was elicited.

A week later, the patient's appetite had definitely improved and the patient, with encouragement, was also eating a little meat. After 12 days, oral 'becosym', 5 ml., was substituted for the parenteral dose.

Three weeks after the start of treatment all diarrhoea had ceased. However, the patient remained a little disorientated, her appetite began to deteriorate again, and by October 26 her weight, which had risen by 2½ lb., had fallen back to the weight recorded on admission. There followed a period of three weeks during which weight remained stationary and appetite varied greatly from day to day. There was, however, no relapse of the dermatitis, which progressively dwindled.

Two months after admission, in an attempt to induce appetite, soluble insulin was administered 20 minutes before meals, starting with 2 units and gradually increasing the dose. A slight improvement in appetite followed and weight began very slowly to increase. Eight units gave the maximal benefit, but 10 units caused a hypoglycaemic reaction.

The patient was discharged from hospital at the end of January, active and symptom-free, but she had gained only 3 lb. in weight since admission. She was last seen on July 15, 1954, when she had gained a further 9 lb. 14 oz. She was eating a normal diet, supplemented by two 'multivite' tablets daily and was enjoying excellent health. The skin was normal.

Discussion

The Nutrition Committee of the British Medical Association (1950) suggested 6 mg. as the daily requirement of nicotinic acid at this age. Analysis of the patient's recent diet shows a total daily content in the neighbourhood of only 1 mg.

Ten years ago nicotinic acid itself was used in the treatment of pellagra. Nicotinamide is now preferred as it does not have the vasodilatory and other undesirable effects of the former substance. The dosage is the same, and Bicknell and Prescott (1953) suggest a dose of 300 to 500 mg. daily in a severe adult case.

In the present case, treatment produced only a temporary increase in appetite and real improvement did not begin until meals were preceded by insulin. This was used with caution, for pellagrins are believed to be hypersensitive to insulin, suffering hypoglycaemic reactions more readily than normal persons (Mainzer, 1949).

Summary

A case of pellagra in an English child of preschool age is described.

I have to thank Dr. D. W. Beynon for permission to publish this case, and Mr. J. Clark for photographs.

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PAEDIATRIC SOCIETIES IN THE BRITISH ISLES

The following is a list of paediatric societies and their principal officers at the time of compilation. Alterations when they occur, information on new societies or any omissions from this should be passed to the Secretary of the British Paediatric Association.

I: National

British Paediatric Association
President: Professor Stanley Graham
Secretary: Dr. P. R. Evans
The Hospital for Sick Children,
Great Ormond Street,
London, W.C.1.

The Royal Society of Medicine, Section of Paediatrics
President: G. H. Macnab, Esq., F.R.C.S.
Secretaries: Dr. U. James
Dr. Leslie Scott
The Royal Society of Medicine,
1 Wimpole Street,
London, W.1.

The British Association of Paediatric Surgeons
President: Denis Browne, Esq., F.R.C.S.
Secretary: D. J. Waterston, Esq., F.R.C.S.
The Hospital for Sick Children,
Great Ormond Street,
London, W.C.1.

The Scottish Paediatric Society
President: Professor C. McNeil
Secretary: Dr. J. H. Hutchison
Royal Hospital for Sick Children,
Yorkhill,
Glasgow, C.3.

Scottish Surgical Paediatric Club
Secretary: Mr. W. M. Dennison, F.R.C.S.E.
Royal Hospital for Sick Children,
Yorkhill,
Glasgow, C.3.

Ulster Paediatric Society
Chairman: Dr. M. L. Frazer, F.R.C.P., F.R.C.S.(I.)
Secretary: Dr. W. A. B. Campbell,
19 Adelaide Park,
Belfast.

Irish Paediatric Association
President: Dr. Victoria Coffey
St. Kevin's Hospital.
Secretary: Dr. Sheamus Dundon
9 Fitzwilliam Place,
Dublin.

Welsh Paediatric Club
Secretary: c/o Professor A. G. Watkins
Department of Child Health,
Llandough Hospital,
Penarth,
Glam.

II: Regional

The Aberdeen Child Health Society
President: Professor J. Craig
Secretary: Dr. Norman S. Clark
374 Great Western Road,
Aberdeen.

Caernarvonshire and Anglesey Paediatric Club
President: Mr. Leonard C. Lancaster, M.A., M.B., F.R.C.S.
Secretary: Dr. M. Slater
2 Brynteg Terrace,
Bangor,
North Wales.

Kent Paediatric and Child Health Society
President: Dr. P. R. Evans
Secretary: Dr. E. L. Huppert
Health Department,
County Hall,
Maidstone, Kent.

The Leeds Regional Paediatric Club
President: Dr. E. C. Benn
Secretary: Dr. R. J. Pugh
Department of Child Health,
Medical School,
Leeds, 1.

Manchester Paediatric Club
President: Dr. A. Holzel
Secretary: Professor W. Gaisford
St. Mary's Hospital,
Whitworth Park,
Manchester, 13.

Midland Regional Paediatric Society
President: Dr. F. Braid
Secretaries: Dr. W. Cant
Children's Hospital,
Ladywood Road,
Edgbaston,
Birmingham, 16.
Dr. M. E. Macgregor
Warwick Hospital,
Lakin Road,
Warwick.

Sheffield Regional Paediatric Society
President: Dr. J. Vernon Braithwaite
Secretary: Dr. R. R. Gordon
58 Nether Edge Road,
Sheffield, 7.

South West Regional Paediatric Club
President: Professor A. V. Neale
Secretary: Dr. J. Apley
Department of Child Health,
Children's Hospital,
St. Michael's Hill,
Bristol, 2.

The Liverpool Paediatric Club
President: Professor N. B. Capon
Secretary: Dr. R. M. Todd
Department of Child Health,
Alder Hey Hospital,
Liverpool, 12.

S.E. Metropolitan Regional Paediatric Society
President: Dr. R. Mac Keith
Secretary: Dr. S. D. V. Weller
50 Southborough Road,
Bickley, Kent.

BOOK REVIEWS

L'accrescimento umano. By G. DE TONI. (Pp. 240. Lira 1,000-) Brescia, Italy: La Scuola.

Professor de Toni's book is one of a series dealing with the formative years of life, and it is addressed not only to doctors but to educationists and psychologists as well. In considering human growth the author has interpreted his subject widely, and he takes the reader by gentle stages from the conception of the embryo to the pubertal years and the completion of physical development. Not only the physical aspect of the subject is considered, however, but the causes and hormonal direction of growth and the psychological aspects of the total human being receive considerable attention. Somatotypes are explained diagrammatically, and there is an appendix of photographs illustrating different types of product of the human race.

A wealth of information is assembled in this short book, and it should be particularly useful as a background of knowledge for those concerned with the bringing up and education of children.

Infant Feeding and Feeding Difficulties. By PHILIP EVANS and RONALD MAC KEITH. Second edition. (Pp. x+277; 66 illustrations. 12s. 6d.) London: J. & A. Churchill, 1954.

That a second edition of this practical guide to the rearing of infants should have been called for three years after the first publication of the book shows that a real need for such a handbook existed. The lay-out of the book is little altered but parts have been revised and the clarity of some of the instructions, particularly on artificial feeding, have been greatly enhanced. These alterations have meant a small increase in the size of the book but the reader will gladly put up with the necessity for reading a little more for the additional ease of understanding.

As with the first edition, this new one will commend itself to all readers by its directness of thought and clarity of expression and last, but not least, by the ease with which information can be extracted from it. With its modest size and price it will continue to appeal to that great public of all professions who are concerned with bringing up babies.

Paediatrics for the Practitioner. Edited by WILFRID GAISFORD and REGINALD LIGHTWOOD. (Three volumes illustrated, plus complete index volume. £13 10s. per set.) London: Butterworth. 1953-1955.

These beautifully produced volumes are as much credit to the publishers as their contents are to the eminent team of paediatricians and others who have been co-opted from all over the world to compose *Paediatrics for the Practitioner*.

Whereas the many excellent textbooks of paediatrics available are generally aimed at the paediatrician, the target of Gaisford and Lightwood is, as the title indicates, essentially the family doctor; while, therefore, there is an almost complete coverage of paediatric subjects, each is dealt with mainly from the point of view of what can be done by the family doctor in the patient's own home. The depressing size of the three volumes of subject matter is to some extent countered by the inclusion of a separate index volume, itself running to no less than 119 pages, the primary use of which in most instances will enable one to select the requisite volume for reading up a particular subject. A foreword says that advances in paediatrics will be dealt with in special supplementary volumes.

It will be interesting to see if the simplified presentation of its subject will seduce practitioners from their accustomed textbook of paediatrics to this monumental work —with its monumental price. There can be no doubt that *Paediatrics for the Practitioner* is as authoritative as any similar work and as up to date as any production of this kind can be. Indeed, editors, authors and publishers must have worked in very close and willing collaboration to have enabled the four volumes to appear in such a short space of time; all are deserving of congratulations.

Diseases of Infancy and Childhood, Vols. I and II. Second edition. Edited by LEONARD PARSONS and SEYMOUR BARLING, assisted by Clifford G. Parsons. (Pp. xli+2,075; 338 figures, 4 coloured plates. 168s.) Oxford University Press (London: Geoffrey Cumberlege). 1954.

This is a book of 2,075 pages, on good paper, weighing just over half a stone.

There can be few textbooks which have experienced so many vicissitudes in their preparation. The previous edition was printed in 1933. Preparations for the second edition were far advanced in 1939, when war stopped further work. After the war different contributors had to be found, and in 1950 much of the script was in the galley proof stage when Sir Leonard Parsons died, and the work was held up once more. The present editors deserve sincere congratulations for finally completing the book in the face of great difficulties. The various revisions of the script which have of necessity been made have probably done much to bring about the very high quality of the final product, which is a great tribute to the present editors.

As the editors regretfully state in the preface, some of the treatments recommended are now out of date. These concern almost entirely the use of antibiotics, cortisone, and a few specific drugs such as those for threadworms, and it involves only a very small fraction of the book. It is not a vital matter. It is virtually impossible to prepare a text of this magnitude which will be up to date by the time it is published. As long as that

fact is realized, it will detract little from the very real value of these volumes.

It will always be impossible to produce a book with the whole of which everyone will agree. When a book is criticized, the fault may lie in the book or in the critic. This book is remarkably devoid of what American reviewers of British books rightly term 'quaint treatments'. There are a few, but very few. Few physicians will agree with the statement that phimosis causes hydronephrosis, masturbation or enuresis.

It is a pity that the common practice of giving diet sheets for normal children is perpetuated. Who really measures out 1 oz. of minced meat or fish and 2½ oz. of milk pudding for the 12- to 18-month-old child?

The weakest section of the book is that devoted to child psychiatry, neuroses and psychoneuroses. Who really believes that contraceptives may cause mental deficiency? That nail-biting is caused by worms, chronic dyspepsia or nasal catarrh? That enuresis should be treated by the removal of tonsils, by ultra-violet light, massage, tonics, a plain and unstimulating diet, the avoidance of bulky starch meals, a flannel binder round the loins, or an appliance for preventing the child sleeping on his back? That 'a baby with flatulence may smile during sleep'? That 'fidgeting habits' are due to decayed teeth, infected tonsils, enlarged glands, chronic nasopharyngeal catarrh, or conjunctivitis, or that it should be treated by arsenic, massage, ultra-violet light, or a mixture of hydrobromic acid and nux vomica?

On looking at the index no mention could be found of accidents or accident prevention: destructiveness, quarrelsomeness, jealousy, pleurodynia, frequency of micturition, normal puberty, abdominal pain, and, surely one of the commonest of all symptoms in children, poor appetite or anorexia in the well child due to forcing food on him. It would be useful if, in the next edition, those and other common symptoms in children were discussed in detail in sections of their own.

These criticisms concern a very small section of the book. They should certainly not deter anyone from buying it, for it contains very many first-class sections, and very little indeed of poor quality. Amongst many excellent sections, that of F. J. W. Miller and the late Sir James Spence on neonatal diseases is outstanding.

One very much hopes that the present editors will see to it that few years elapse before a third edition is published. It would be most regrettable if the book were allowed to lapse when it has reached such a very high standard. It is the reviewer's considered opinion that this book is a great credit to the Birmingham school, and that it will remain a fitting and brilliant tribute to its designer, Sir Leonard Parsons.

Modern Mothercraft: A Guide to Parents. Third edition. By HELEN DEEM and NORA P. FITZGIBBON. (Pp. 241. Price not stated.) Dunedin: Royal New Zealand Society for the Health of Women and Children. 1954.

This revised edition of a rightly popular handbook is notable because it records the abandoning of 'percentage feeding' in what was its country of origin. Milk mixtures are now made stronger than the old 'equal parts' formula from the fourteenth day of life, and although even now undiluted milk is not allowed until the ninth month, the present step forward must be welcomed. The idea of 'humanized' milk has therefore been discarded. The rigidity of the older feeding programmes has also been modified by a somewhat grudging reference to self-demand feeding, but this apart there is in many sections a welcome modern outlook in many aspects of the mother-baby relationship. A section on prevention of accidents in the home is full of wise advice.

Cystic Fibrosis of the Pancreas in Infants and Children. By CHARLES D. MAY. (Pp. 93; 16 figures. 21s. 6d.) Oxford: Blackwell Scientific Publications. 1954.

This monograph follows on the heels of Bodian's *Fibrocystic Disease of the Pancreas* which it resembles in everything but size, price and number of illustrations. In a small space Dr. May has managed to condense all that is known about this very interesting condition, and if each separate disease needs its own handbook this will be most adequate for cystic fibrosis of the pancreas. No dogmatic standpoint is adopted concerning the aetiology of the disease and not all will agree with the author in dismissing so summarily the estimation of the anti-thrombin titre of the blood in diagnosis; yet the book must have been in the hands of the printers for a considerable time and presumably a second edition will amplify this point.

The monograph is beautifully printed and bound and must be almost the lightest medical book to be produced for years.

Manuel Pratique de Vaccination par le B.C.G. By R. MANDE; foreword by Robert Debré. (Pp. 200; 13 plates, 4 in colour. Fr. frs. 950.–) Published by Le Centre International de l'Enfance. Paris: Masson et Cie. 1954.

This little paper-backed book of 200 pages, the sixth monograph published by the International Children's Centre in Paris, is an excellent practical guide for anyone having to undertake B.C.G. vaccination in children because it is the outcome of the considerable personal experience of the author in the B.C.G. clinic associated with the Children's Centre.

The first six sections each concludes with a full summary of the main points discussed. The details of the various techniques are well set out, the complications are discussed, with suggestions as to prevention and treatment, and the importance of adequate follow-up is stressed. The vexed questions of the innocuousness of B.C.G. and exogenous tuberculous infection after vaccination are fully considered and, needless to say, Calmette is once again vindicated. The presentation, however, is fair and reasoned. The seventh and final section is a recapitulation of the essential practical principles and is clear and concise.

There is an admirable foreword by Professor Debré. Fourteen coloured and 26 monotone illustrations—all very well reproduced—add to the clarity of the work. The references, though few, are valuable and up-to-date.

Pathologie Infantile. Second edition; in two volumes. Edited by R. DEBRÉ, E. LESNÉ and P. ROHMER. (Pp. 2,286; 409 figures. Fr. frs. 17,500.–) Paris: G. Doin & Cie and Masson & Cie. 1954.

This is a cross between the textbook of Debré and Lelong and a *Recent Advances in Paediatrics*, and as it deals with the whole picture of disease in childhood from causation to treatment the word *pathologie* in the title may be slightly misleading to the English eye. In spite of the size of the volumes, it is a comment on the growing bulk of paediatric knowledge that no subject is considered exhaustively but that the reader is led through the different illnesses with almost breathless speed. To anyone accustomed to the English textbook lay-out it is rather difficult to find one's way around these two books. First, the table of contents appears at the end of the volume and, secondly, only Volume II has an index, and this in places is sketchy.

It is still open to doubt whether reference books such as these should not appear in loose-leaf form so that sections may be brought up to date by the issue of a supplement as is the case with Debré and Lelong's *Pédiatrie*; and one cannot help wondering if there is in the French literature room for both *Pathologie Infantile* and *Pédiatrie*. The labour involved in bringing *Pathologie Infantile* up to date as new advances are made compares unfavourably with the simplicity of issuing new sections of *Pédiatrie*; and undoubtedly this latter method of avoiding the need for new editions must, in view of rising costs in every direction, be a major development of the near future.

Cleft Palate and Speech. Third edition. By MURIEL E. MORLEY. (Pp. 173. 17s. 6d.) London and Edinburgh: E. & S. Livingstone. 1954.

This book presents a review of hare lip and cleft palate from almost every aspect, and is clearly the result of wide experience and study.

The preliminary chapters on the anatomy and physiology of the palate and mechanism of oro-nasal closure lead on to a comprehensive review of the evolution of cleft palate surgery and the problems associated with feeding and speech, and finally with treatment.

The author has emphasized the importance of close cooperation between surgeon, orthodontist and speech therapist in these cases, and although this book is of essential interest to the professional speech therapist, it could be read with profit by all who are concerned with this difficult problem.

The Mentally Subnormal Child. World Health Organization Technical Report Series No. 75: report of a Joint Expert Committee. (Pp. 46. 1s. 9d.) London: H.M. Stationery Office. 1954.

This is a pamphlet of 46 pages concerned with the diagnosis and disposal (including treatment) of children who in England would be called (in the terms of the Education Act of 1944) educationally subnormal and ineducable. The section on diagnosis is the shorter and less adequate, particularly in that it does not mention the problem of the differential diagnosis of defect and psychosis. The larger section (33 pages) describes the existing arrangements in some countries for dealing with such children, outlines what, in the opinion of the committee, are their principal needs, and discusses at length the best ways in which their needs can be met. The last section on the need for the coordination of the many services involved in the welfare of a mentally subnormal child is perhaps the most important. The report, which is very well written, should win the approval of all relevant workers. Its recommendations are clear and precise without being dogmatic. A valuable refresher course for all people concerned with children whether in medicine, education or the social services.

Herzkrankheiten im Säuglingsalter. By E. ROSSI. (Pp. xvi+373; 198 figures. DM. 65.–) Stuttgart: Georg Thieme Verlag. 1954.

This monograph, with a foreword by Professor Fanconi, comes from the Kinderspital in Zurich, and this fact will ensure a good reception for it. The investigation and diagnosis of heart disease and heart malformation have advanced to paramount importance and it is from this standpoint that Dr. Rossi has written his book. A short introductory chapter on the normal infant's heart is followed by a rather potted consideration of all the congenital malformations one after the other. In the third chapter various types of myocarditis are considered and from these are separated a group called myocardoses in which infiltration of the heart is involved; in this chapter, too, endocardial fibro-elastosis is quite properly given consideration. Other chapters are on secondary involvement of the heart and on the medical treatment of cardiac insufficiency.

Throughout the monograph there are ample pictures and diagrams to illustrate precisely the author's points, and the various types of disease considered are enlarged by descriptions of his own cases. This book can be wholly recommended.

Practical Fluid Therapy in Pediatrics. By FONTAINE S. HILL. (Pp. 275+xx; 20 figures. 30s.) London and Philadelphia: W. B. Saunders. 1954.

The title of this book is an understatement of the contents. The book opens with a glossary of some 70 terms in common use. In the next chapters the author takes the reader by the hand and introduces him to all the important terms in very simple language. The various mechanisms involved in fluid and electrolyte homeostasis are equally simply displayed and the results of disturbances of the normal equilibrium by disease discussed.

In the next section, repair solutions are described and their use in differing circumstances discussed. Chapters 7 to 13 then deal with individual problems, such as diarrhoea, diabetic coma, burns, surgical conditions, etc.

In each chapter the same general formula is used—a description of the condition, the clinical manifestations, with one or more case reports, 'pathophysiology' (the fluid-electrolyte disturbance), laboratory findings, treatment. In dealing with laboratory findings all useful technical methods are discussed, not simply those relative

to water and electrolytes. Similarly in treatment, nearly as much space is given to general treatment of the condition as is given to the correction of the water-electrolyte disturbances. The final chapters are on techniques of blood taking and fluid administration.

This method of presentation has advantages if it is desired to look up the treatment of one condition, but it does entail much repetition. All through this book the emphasis is on the practical clinical aspects, and one can almost hear the author's sigh of relief as he turns from the theoretical section to the clinical sections.

For a book of this size, there is very little to take exception to, and these few criticisms are only of minor points.

Deutsche Nachkriegskinder. By C. COERPER, W. HAGEN and H. THOMAE. (Pp. xii+545; 175 tables. DM. 33.–) Stuttgart: Georg Thieme Verlag. 1954.

This book contains the first results of a longitudinal study of the development of children in post-war Germany. Centres in Frankfurt, Nuremburg, Stuttgart, Bonn, Remscheid and Grevenbroich have combined to collect and collate a vast amount of clinical material which this book presents and analyses. Less attention is paid to physical than to mental and psychological development and the thoroughness with which the data are worked out is admirable.

It is interesting to know that longitudinal studies, like those at present being undertaken in this country by the Child Study Centre, are bearing their fruits in other countries, and we can look forward to similar reports from these German trials in the future. Much of the present book is concerned with the methods employed in the study, and the authors will be able to contract subsequent monographs by omission of much of this section of the present book; this will reduce size without detracting from merit.

Thieme have maintained their expected standard of production.

Deprived Children—The Merstham Experiment. A Social and Clinical Study. By HILDA LEWIS; foreword by Sir Arthur Ellis and Dr. C. P. Blacker. (Pp. xvii+163. 9s. 6d.) Published for Nuffield Foundation by Oxford University Press (London: Geoffrey Cumberlege). 1954.

Who does not sometimes envy his house physician on the grounds that H.P.s spend all their time doing 'real' medicine, unlike ourselves who spend so much time dealing with housing authorities, food officers, regional boards, enthusiastic but ill-informed laymen all too willing to help, headmasters all too unwilling to take deserving children? All very different from our vague memory of a clinical Garden of Eden without serpentine social problems.

Dr. Lewis's book is very relevant to what the house officer of today knows to be 'real' medicine and to the common worries about the best management of children. It deals with the Merstham experimental reception centre for deserted, maladjusted, homeless, neglected children. Five hundred children were admitted there between 1947 and 1950, and their family background studies and their physical and mental health observed, so that the most suitable homes or schools could be chosen. The Curtis Committee suggested that all children received into care by a public authority should go to such a centre. In practice most of them are in public care because of temporary illness of a parent, but at least a third need the careful placing that only well-staffed and well-run placement centres can give.

The book tells of children who had repeatedly been returned to the authority from successive foster homes, more disturbed each time, and it was partly to avoid such mal-placements that the Merstham Centre was started. Dr. Lewis has clearly established the value of such centres.

Dr. Lewis's follow-up studies also contribute to our knowledge of the causes of behaviour disorders, for she confirms that in general parental rejection tends to lead to unsocialized, aggressive behaviour, while neglect leads to socialized delinquency and constraint tends to produce neurotic behaviour.

All children's doctors should read at least the summary of Chapter 5 and the whole of Chapter 6 (General Reflections), and they should get their lady almoners to read these too. When can a child's needs be assessed without admission? When is a residential school a preferable placement to a foster home? These and other questions are discussed in a way that will help us to deal with these problems of present paediatrics and help us to understand how the child's officer and other agencies are trying to help deprived children.

Elements of Pediatric Anesthesia. By C. R. STEPHEN. (Pp. xv+109; 25 figures. 25s.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1954.

This monograph on paediatric anaesthesia is the latest in the series of American lectures in anaesthesiology. The views expressed are sound and the practising anaesthetist who does not encounter children very often in his daily work will obtain a great deal of practical help.

The main theme is safety, which is well illustrated by the recommended technique of open ether for bronchography and bronchoscopy. Although this technique does not avoid the explosion hazard, in the hands of the average doctor this is a calculated risk and is probably less than the dangers associated with other techniques.

As well as covering most aspects of paediatric anaesthesia, there are sections on blood transfusion, oxygen therapy and asphyxia of the newborn, all of which are concise and factual. If there is a need in this country for a handbook on paediatric anaesthesia, this one fulfils the purpose adequately.

La Coqueluche. By J. MARIE, G. SÉE and E. ELIACHAR. (Pp. 292; 47 figures. Fr. frs. 2,000.–) Paris: Expansion Scientifique Française. 1954.

Les Méningo-Encéphalites Lymphocytaires chez L'Enfant. By A. GAUTIER. (Pp. 172. Fr. frs. 1,200.–) Paris: Expansion Scientifique Française. 1954.

The difference in price between these two volumes must

be accounted for by the fact that the monograph on whooping cough is elegantly produced and bound, while that on meningo-encephalitis is a utilitarian production with a paper cover. Apart from this the two monographs are remarkably similar in approach to their subjects of whooping cough and benign lymphocytic meningitis respectively, and both contain introductions by that indefatigable writer of prefaces, Professor Robert Debré.

The main interest in the consideration of whooping cough at the moment turns on prevention and treatment, and in the book under review the difficulties of efficient vaccine preparation are discussed, and there is an informative section on the pros and cons of immunization in the neonatal period, together with some substantiation of the hypothesis that the newborn infant is serologically immature. Compared with the practice of other countries the authors recommend later vaccination both for whooping cough and with combined prophylactics. The section on the treatment of established whooping cough is as indeterminate as the treatment of the condition itself, and indeed cannot well be otherwise.

Les Meningo-encéphalites Lymphocytaires chez l'Enfant is a praiseworthy attempt to bring together the vast mass of data concerning what in this country is called benign lymphocytic meningitis or aseptic meningitis, yet the subject is wider than this in that the leptospiroses are considered; in fact almost every non-bacterial condition affecting the central nervous system is considered. The author concludes rather sadly that although a great deal of progress has been made in the differentiation of the various diseases during the last 30 years, a great deal remains still unknown of the mechanism whereby the diseases are brought about; and further, he indicates how much our diagnostic skill is in advance of our ability to treat what we can diagnose.

Atlas of Congenital Cardiac Disease. By MAUDE ABBOTT. (Pp. 62; illustrated. $5.00.) New York: The American Heart Association. 1936.

This is a facsimile reproduction of a book so famous that to review it would be an impertinence. The American Heart Association has rendered a service to the study of congenital heart disease by making available a work of reference which has long been out of print.

The Year Book of Pediatrics, 1954-55. Edited by SIDNEY S. GELLIS. (Pp. 431; 112 figures. 45s.) Chicago: The Year Book Publishers, Inc., Distributed in the U.K. by Interscience Publishers Ltd., London. 1954.

This year book follows the usual lay-out and contains abstracts of some 330 of the more—and less—important papers dealing with problems of child health and disease published during the 12-months period under review. Many of the abstracted papers are followed by *ex cathedra* pronouncements by other workers in the same field.

This is a quite excellent book for those not in touch with paediatric literature to discover what has been going on during the previous 12 months, and a welcome improvement is to be found in the increased number of non-American papers abstracted, the book assuming thereby a far less parochial appearance. Production, printing and binding maintain the usual high standards and, for the wealth of information contained, the book is very good value for the money.

Growth and Development of Children. Second edition. By ERNEST H. WATSON and GEORGE H. LOWREY. (Pp. 296; 70 figures. 53s.; $7.00.) Chicago: The Yearbook Publishers Inc. (Distributed in U.K. by Interscience Publishers Ltd., London.) 1954.

The fact that this book has been reprinted and has now gone into a second edition within three years of the publication of the first is proof that it is appreciated by those for whom it is primarily intended, viz., students and those working for paediatric examinations. The reasons for this are obvious, since the authors write clearly, summarize much recent American data, and modestly refrain from introducing more than a minimum of original ideas or controversial discussion. In fact, almost all the numerous tables and diagrams are derived from orthodox sources and the references demand no knowledge of any language but English; there are very few which require access to other than the American literature, or suggest the historical background from which this work has stemmed. It is perhaps this parochialism which will make the book unsatisfying to the more critical reader. The section on 'behavioral development', for instance, contains no reference to the work of Isaacs, Klein, the Freuds and the Viennese school. The book can be recommended as a useful if somewhat pedestrian summary of current American work, but not as a balanced introduction to the subject as a whole.

Genetica Medica: Ium Symposium Internationale Geneticae Medicae, September 6-7, 1953. A collection of monographs edited by LUIGI GEDDA. (Pp. xxviii+468; 168 figures. Lira 5,000.) Rome: Edizioni del' Istituto Gregorio Mendel. 1954.

Somewhat belatedly, this book records the papers contributed to the First International Symposium of Medical Genetics, held in Rome in September, 1953. The occasion was the official inauguration in that city of the splendid new Gregor Mendel Institute for the study of medical genetics and twins. The papers are written in Italian, French, German and English and give a good cross-sectional view of the development of medical genetics in Europe. England is represented by a paper by Dr. P. L. Mollison on 'Haemolytic Disease of the Newborn'. Other papers of paediatric interest are those on skeletal abnormalities, juvenile diabetes, sickle-cell anaemia and poliomyelitis. In addition, there are included translations of an authoritative address by Pope Pius XII on the problems involved in eugenics and genetic counselling which will be helpful to any physician who may be consulted by Roman Catholic patients who run a risk of having genetically determined abnormalities in their children.